EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

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European Association of Urology

EANM European Association of Nuclear Medicine — Biomedical Imaging and Therapy for Personalized Healthcare

SIOG International Society of Geriatric Oncology

European Society of Urogenital Radiology

ESTRO European Society for Radiotherapy & Oncology

EUROPA UOMO The Voice of Men with Prostate Cancer in Europe

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1. INTRODUCTION

1.1 Aims and scope

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, a pathologist, a geriatrician and a patient representative.

All imaging sections in the text have been developed jointly with the European Society of Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM). Representatives of the ESUR and the EANM in the PCa Guidelines Panel are (in alphabetical order): Dr. A. Farolfi, Dr. D. Oprea-Lager, Prof.Dr. O. Rouvière and Dr. I.G. Schoots.

All radiotherapy (RT) sections have been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO in the PCa Guidelines Panel are (in alphabetical order): Prof.Dr. A.M. Henry, Prof.Dr. M.D. Mason and Prof.Dr. T. Wiegel.

The International Society of Urological Pathology is represented by Prof.Dr. T. van der Kwast.

Dr. S. O'Hanlon, consultant geriatrician, representing the International Society of Geriatric Oncology (SOIG) contributed to the sections addressing life expectancy, health status and quality of life in particular.

Dr. E. Briers, expert Patient Advocate Hasselt-Belgium representing the patient voice as delegated by the European Prostate Cancer Coalition/Europa UOMO.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/prostate-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available [1, 2] as are a number of translations of all versions of the PCa Guidelines. All documents can be accessed on the EAU website: http://uroweb.org/guideline/prostate-cancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU PCa Guidelines were first published in 2001. This 2022 document presents a limited update of the 2021 EAU-EANM-ESTRO-ESUR-ISUP-SIOG PCa Guidelines publication.

1.4.2 Summary of changes

The literature for the complete document has been assessed and updated based upon a review of all recommendations and creation of appropriate GRADE forms. Evidence summaries and recommendations have been amended throughout the current document and several new sections have been added.

All chapters of the 2022 PCa Guidelines have been updated. New data have been included in the following sections, resulting in new sections, and new and revised recommendations:

- **4.3 Clinically significant prostate cancer**
- *4 5.1.2.4. Risk assessment to determine the need for biopsy*
- *4 5.2.1.2 Repeat PSA testingTable 5.5: Risk data table of clinically significant prostate cancer (csPCa), related to PI-RADS score and PSA-D categories in biopsy-naive men, clinically suspected of having significant disease*
- Section 5.2.7.1.4 Towards 'extended' MRI-directed biopsy?

5.2.3.4 Guidelines for risk-assessment of asymptomatic men

Recommendation	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination, repeat the PSA test prior to further investigations.	Weak

5.2.8 ***Summary of evidence and guidelines for prostate biopsies***

Summary of evidence	LE
Literature review including multiple biopsy schemes suggests that a 10 to 12-core scheme is optimal in the majority of initial and repeat biopsy patients, dependent on prostate size. These biopsy schemes should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [3].	3
A systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%).	2
Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique (cognitive guidance, US/MR fusion software or direct in-bore guidance) over the other.	2

Recommendations	Strength rating
At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc and 10 to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive.	Strong
Transperineal biopsies are preferred over transrectal biopsies.	Strong
Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak

5.2.8.2.1 Recommended terminology for reporting prostate biopsies

Recommendation	Strength rating
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern.	Strong

5.3.5 ***Summary of evidence and guidelines for staging of prostate cancer***

Summary of evidence	LE
PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management.	1b

Recommendation	Strength rating
High-risk localised disease/locally advanced disease	
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

- 6.1.4.1.1.3.4. Radiopharmaceutical therapy

6.1.6 ***General guidelines for the treatment of prostate cancer***

Recommendations	Strength rating
Surgical treatment	
Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined into a nomogram).	Weak

Radiotherapeutic treatment	
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or intermediate-risk disease with ISUP grade 2 and ≤ 33% of biopsy cores involved.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10-20 ng/mL.	Weak
Offer LDR or HDR brachytherapy boost combined with IMRT /VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak

- 6.2.1.2.1 ADT monotherapy

6.2.1.3 Summary of evidence and guidelines for the treatment of low-risk disease

Summary of evidence	LE
Systematic biopsies have been scheduled in AS protocols, the number and frequency of biopsies varied, there is no approved standard.	NR

Recommendations	Strength rating
Active surveillance (AS)	
Selection of patients	
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed	Weak
Follow-up of patients	
Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
In case of PSA progression or change in DRE or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
Active treatment	
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to patients with low-risk PCa and good urinary function.	Strong

6.2.2.5 Guidelines for the treatment of intermediate-risk disease

Recommendations	Strength rating
Active surveillance (AS)	
Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA <10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP grade group 3 disease must be excluded from AS protocols.	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
Offer low-dose rate brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Weak
Offer high-dose rate brachytherapy boost combined with IMRT/VMAT plusIGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	Weak

6.2.3.4 Guidelines for radical treatment of high-risk localised disease

Recommendation	Strength rating
Radiotherapeutic treatment	
In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak

6.2.4.5 Guidelines for radical treatment of locally-advanced disease

Recommendation	Strength rating
Radiotherapeutic treatment	
Offer patients with locally advanced disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or ≥ 2 high-risk factors (cT3–4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong

6.3.4.4 Summary of evidence and guidelines for imaging in patients with biochemical recurrence

Summary of evidence	LE
After RP there is no specific PSA threshold defining recurrence.	NR

6.4.9 ***Guidelines for the first-line treatment of metastatic disease***

Recommendations	Strength rating
Offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong

6.5.15 ***Guidelines for systematic treatments of castrate-resistant disease***

Recommendation	Strength rating
Novel agents	
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

2. METHODS

2.1 Data identification

For the 2022 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the PCa Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between May 1st 2020 and April 14th 2021. A total of 2,536 unique records were identified, retrieved and screened for relevance resulting in 193 new publications having been included in the 2022 print. A detailed search strategy is available online: https://uroweb.org/guideline/prostate-cancer/?type=appendices-publications.

Changes in recommendations were only considered on the basis of high-level evidence (i.e. systematic reviews with meta-analysis, randomised controlled trials [RCTs], and prospective comparative studies) published in the English language. A total of 193 new references were added to the 2022 PCa Guidelines. Additional information can be found in the general Methodology section of this print and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [4, 5]. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address. In addition, the International Society of Geriatric Oncology (SIOG), the European Society for Radiotherapy & Oncology (ESTRO), the European Society for Urogenital Radiology (ESUR), the European Association of Nuclear Medicine (EANM) and the International Society of Urological Pathology (ISUP) have endorsed the PCa Guidelines.

2.2 Review

All RT sections from the 2021 print were peer-reviewed prior to publication, as were Sections 5.4 (Evaluating life expectancy and health status) and Chapter 8 (Quality of life). Publications ensuing from systematic reviews have all been peer-reviewed.

2.3 Future goals

Results of ongoing and new systematic reviews will be included in the 2022 update of the PCa Guidelines:

- A systematic review on progression criteria and quality of life (QoL) of patients diagnosed with PCa;
- A systematic review assessing the performance of risk stratification tools incorporating imaging, biomarkers, biopsy involvement and/or MRI-targeted biopsies, compared to the classical risk classifications (d'Amico, EAU, CAPRA and NCCN) recommended in current guidelines for predicting biochemical recurrence, metastasis or death after local treatment for prostate cancer. Are the new stratification tools preferred above the classical risk classifications?
- A systematic review assessing the outcomes of brachytherapy boost combined with external beam RT for PCa.
- Care pathways for the various stages of PCa management are being developed. These pathways will, in due time, inform treatment flowcharts and an interactive app.
- Assessment of individual patient life expectancy – development of a calculator.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020 [8, 9]. The frequency of autopsy-detected PCa is roughly the same worldwide [10]. A systematic review of autopsy studies reported a prevalence of PCa at age < 30 years of 5% (95% confidence interval [CI]: 3–8%), increasing by an odds ratio (OR) of 1.7 (1.6–1.8) per decade, to a prevalence of 59% (48–71%) by age > 79 years [11].

The incidence of PCa diagnosis varies widely between different geographical areas, being highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively), largely due to the use of prostate-specific antigen (PSA) testing and the aging population. The incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively), but rising [12]. Rates in Eastern and Southern Europe were low but have also shown a steady increase [9, 10]. Incidence and disease stage distribution patterns

follow biological-, genetic-, and/or lifestyle factors, but are also influenced by (inter)national organisations' recommendations on screening and diagnosis (see Section 5.1) [13].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (Caribbean: ASR of 29 and Sub-Saharan Africa: ASRs ranging between 19 and 14), intermediate in the USA and very low in Asia (South-Central Asia: ASR of 2.9) [9].

3.2 Aetiology

*3.2.1 **Family history/hereditary prostate cancer***

Family history and ethnic background are associated with an increased PCa incidence suggesting a genetic predisposition [14, 15]. Only a small subpopulation of men with PCa have true hereditary disease. Hereditary PCa (HPCa) is associated with a six to seven year earlier disease onset but the disease aggressiveness and clinical course does not seem to differ in other ways [14, 16].

In a large USA population database, HPCa (in 2.18% of participants) showed a relative risk (RR) of 2.30 for diagnosis of any PCa, 3.93 for early-onset PCa, 2.21 for lethal PCa, and 2.32 for clinically significant PCa (csPCa) [17]. These increased risks of HPCa were higher than for familial PCa (≥ 2 first- or second-degree relatives with PCa on the same side of the pedigree), or familial syndromes such as hereditary breast and ovarian cancer and Lynch syndrome. The probability of high-risk PCa at age 65 was 11.4% (vs. a population risk of 1.4%) in a Swedish population-based study [18].

3.2.1.1 Germline mutations and prostate cancer

Genome-wide association studies have identified more than 100 common susceptibility loci contributing to the risk for PCa [19-21]. Clinical cohort studies have reported rates of 15% to 17% of germline mutations independent of stage [22, 23]. Giri *et al.*, studied clinical genetic data from men with PCa unselected for metastatic disease undergoing multigene testing across the US [22]. The authors found that 15.6% of men with PCa have pathogenic variants identified in genes tested ([BReast Cancer genes] *BRCA1, BRCA2, HOXB13, MLH1, MSH2, PMS2, MSH6, EPCAM, ATM, CHEK2, NBN,* and *TP53*), and 10.9% of men have germline pathogenic variants in DNA repair genes (see Table 5.2). Pathogenic variants were most commonly identified in *BRCA2* (4.5%), *CHEK2* (2.2%), *ATM* (1.8%), and *BRCA1* (1.1%) [22].

Castro *et al.*, found a carrier rate of 16.2% in unselected patients at diagnosis of metastatic castrate-resistant PCa (mCRPC) who were screened for DNA damage repair (DDR) mutations in 107 genes [24].

Nicolosi *et al.*, reported frequency and distribution of positive germline variants in 3,607 unselected PCa patients and found that 620 (17.2%) had a pathogenic germline variant [23]. Among unselected men with metastatic PCa, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes [25].

Targeted genomic analysis of genes associated with an increased risk of PCa could offer options to identify families at high risk [26, 27].

Nyberg *et al.,* presented results of a prospective cohort study of male *BRCA1* and *BRCA2* carriers and their PCa risk confirming *BRCA2* association with aggressive PCa [28]. Castro *et al.*, analysed the outcomes of 2,019 patients with PCa (18 *BRCA1* carriers, 61 *BRCA2* carriers, and 1,940 non-carriers). Prostate cancers with germline *BRCA1/2* mutations were more frequently associated with ISUP ≥ 4, T3/T4 stage, nodal involvement, and metastases at diagnosis than PCa in non-carriers [29]. BRCA-susceptibility gene mutation carriers were reported to have worse outcome when compared to non-carriers after local therapy [30].

In a retrospective study of 313 patients who died of PCa and 486 patients with low-risk localised PCa, the combined *BRCA1/2* and *ATM* mutation carrier rate was significantly higher in lethal PCa patients (6.07%) than in localised PCa patients (1.44%) [31].

The Identification of Men With a Genetic Predisposition to ProstAte Cancer (IMPACT) study, which evaluated targeted PCa screening (annually, biopsy recommended if PSA > 3.0 ng/mL) using PSA in men aged 40–69 years with germline *BRCA1/2* mutations found that after 3 years of screening, *BRCA2* mutation carriers were associated with a higher incidence of PCa, a younger age of diagnosis, and more clinically significant tumours compared with non-carriers [32]. The influence of *BRCA1* mutations on PCa remained unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* non-carriers. Limitations of the IMPACT study include the lack of magnetic resonance imaging (MRI) data and targeted biopsies as it was initiated before that era.

Similarly, Mano *et al.*, reported on an Israeli cohort in which men with *BRCA1* and *BRCA2* mutations had a significantly higher incidence of malignant disease. In contrast to findings of the IMPACT study, the rate of PCa among *BRCA1* carriers was more than twice as high (8.6% vs. 3.8%) compared to the general population [33].

*3.2.2 **Risk factors***

A wide variety of exogenous/environmental factors have been discussed as being associated with the risk of developing PCa or as being aetiologically important for the progression from latent to clinical PCa [34]. Japanese men have a lower PCa risk compared to men from the Western world. However, as Japanese men move from Japan to California, their risk of PCa increases, approaching that of American men, implying a role of environmental or dietary factors [35]. However, currently there are no known effective preventative dietary or pharmacological interventions.

3.2.2.1 Metabolic syndrome

The single components of metabolic syndrome (MetS), hypertension ($p = 0.035$) and waist circumference > 102 cm ($p = 0.007$), have been associated with a significantly greater risk of PCa, but in contrast, having ≥ 3 components of MetS is associated with a reduced risk (OR: 0.70, 95% CI: 0.60–0.82) [36, 37].

3.2.2.1.1 Diabetes/metformin

The association between metformin use and PCa is controversial. At population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never-users (adjusted OR: 0.84, 95% CI: 0.74–0.96) [38]. In 540 diabetic participants of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study, metformin use was not significantly associated with PCa and therefore not advised as a preventive measure (OR: 1.19, $p = 0.50$) [39]. The ongoing Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial assesses metformin use in advanced PCa (Arm K) [40].

3.2.2.1.2 Cholesterol/statins

A meta-analysis of 14 large prospective studies did not show any association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels and the risk of either overall PCa or high-grade PCa [36]. Results from the REDUCE study also did not show a preventive effect of statins on PCa risk [37].

3.2.2.1.3 Obesity

Within the REDUCE study, obesity was associated with lower risk of low-grade PCa in multivariable analyses (OR: 0.79, $p = 0.01$), but increased risk of high-grade PCa (OR: 1.28, $p = 0.042$) [41]. This effect seems mainly explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [42].

3.2.2.2 Dietary factors

The association between a wide variety of dietary factors and PCa have been studied, but there is still a paucity of quality evidence (Table 3.1).

Table 3.1: Main dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [43]. A meta-analysis shows a dose-response relationship with PCa [44].
Coffee	Coffee consumption may be associated with a reduced risk of PCa; with a pooled RR of 0.91 for the highest category of coffee consumption [45].
Dairy	A weak correlation between high intake of protein from dairy products and the risk of PCa was found [46].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [47]. A relation between intake of fried foods and risk of PCa may exist [48].
Tomatoes (lycopenes/ carotenes)	A trend towards a favourable effect of tomato intake (mainly cooked) and lycopenes on PCa incidence has been identified in meta-analyses [49, 50]. Randomised controlled trials comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [51].
Meat	A meta-analysis did not show an association between red meat or processed meat consumption and PCa [52].
Soy (phytoestrogens [isoflavones/ coumestans])	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [53]. Total soy food intake has been associated with reduced risk of PCa, but also with increased risk of advanced disease [54, 55].

Vitamin D	A U-shaped association has been observed, with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [55, 56].
Vitamin E/Selenium	An inverse association of low blood levels of selenium and vitamin E, but mainly nail selenium levels (reflecting long-term exposure) with aggressive PCa have been found [57, 58]. Selenium and Vitamin E supplementation were, however, found not to affect PCa incidence [59].

3.2.2.3 Hormonally active medication

3.2.2.3.1 5-alpha-reductase inhibitors (5-ARIs)

Although it seems that 5-ARIs have the potential of preventing or delaying the development of PCa (~25%, for ISUP grade 1 cancer only), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade PCas, although these do not seem to impact PCa mortality [60-63]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

3.2.2.3.2 Testosterone

Hypogonadal men receiving testosterone supplements do not have an increased risk of PCa [64]. A pooled analysis showed that men with very low concentrations of free testosterone (lowest 10%) have a below-average risk (OR: 0.77) of PCa [65].

3.2.2.4 Other potential risk factors

A significantly higher rate of ISUP ≥ 2 PCa (hazard ratio [HR]: 4.04) was found in men with inflammatory bowel disease when compared with the general population [66]. Balding was associated with a higher risk of PCa death [67]. Gonorrhoea was significantly associated with an increased incidence of PCa (OR: 1.31, 95% CI: 1.14–1.52) [68]. Occupational exposure may also play a role, based on a meta-analysis which revealed that night-shift work is associated with an increased risk (2.8%, p = 0.030) of PCa [69]. Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24, 95% CI: 1.18–1.31) and with aggressive tumour features and worse prognosis, even after cessation [70, 71]. A meta-analysis on Cadmium (Cd) found a positive association (magnitude of risk unknown due to heterogeneity) between high Cd exposure and risk of PCa for occupational exposure, but not for non-occupational exposure, potentially due to higher Cd levels during occupational exposure [72]. Men positive for human papillomavirus-16 may be at increased risk [73]. Plasma concentration of the estrogenic insecticide chlordecone is associated with an increase in the risk of PCa (OR: 1.77 for highest tertile of values above the limit of detection) [74].

A number of other factors previously linked to an increased risk of PCa have been disproved including vasectomy [75] and self-reported acne [76]. There are conflicting data about the use of aspirin or non-steroidal anti-inflammatory drugs and the risk of PCa and mortality [77, 78].

Ultraviolet radiation exposure decreased the risk of PCa (HR: 0.91, 95% CI: 0.88–0.95) [79]. A review found a small but protective association of circumcision status with PCa [80]. Higher ejaculation frequency (≥ 21 times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [81].

To date the current body of evidence will not support a causal relationship between specific (dietary and otherwise) factors and the development of PCa. Consequently, no effective preventative strategies can be suggested.

3.2.3 Summary of evidence for epidemiology and aetiology

Summary of evidence	**LE**
Prostate cancer is a major health concern in men, with incidence mainly dependent on age.	3
Genetic factors are associated with risk of (aggressive) PCa.	3
A variety of dietary/exogenous/environmental factors have been associated with PCa incidence and prognosis.	3
Selenium or vitamin-E supplements have no beneficial effect in preventing PCa.	2a
In hypogonadal men, testosterone supplements do not increase the risk of PCa.	2
No conclusive data exit which could support specific preventive or dietary measures aimed at reducing the risk of developing PCa.	1a

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the development of recommendations for the treatment of these patient populations. Throughout these Guidelines the 2017 Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [82] and the EAU risk group classification, which is essentially based on D'Amico's classification system for PCa, are used (Table 4.2) [83]. The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT). Magnetic resonance imaging and targeted biopsy may cause a stage shift in risk classification systems [84].

Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [82]

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*

[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Clinical T stage only refers to digital rectal examination (DRE) findings; local imaging findings are not considered in the TNM classification. Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1 and the T2 substages. Pathological stages pT1a/b/c do not exist and histopathologically confirmed organ-confined PCas after RP are pathological stage pT2. The current Union for International Cancer Control (UICC) no longer recognises pT2 substages [82].

Of note: the EANM recently proposed a 'miTNM' (molecular imaging TNM) classification, taking into account prostate-specific membrane antigen positron emission tomography–computed tomography (PSMA PET/CT) findings [85]. The prognosis of the miT, miN and miM substages is likely to be better to their T, N and M counterparts due to the 'Will Rogers phenomenon'; the extent of this prognosis shift remains to be assessed as well as its practical interest and impact [86].

4.2 Gleason score and International Society of Urological Pathology 2014 grade

In the original Gleason grading system, 5 Gleason grades (ranging from 1–5) based on histological tumour architecture were distinguished, but in the 2005 and subsequent 2014 International Society of Urological Pathology (ISUP) Gleason score (GS) modifications Gleason grades 1 and 2 were eliminated [87, 88]. The 2005 ISUP modified GS of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern, if two are present. If one pattern is present, it needs to be doubled to yield the GS. For three grades, the biopsy GS comprises the most common grade plus the highest grade, irrespective of its extent. The grade of intraductal carcinoma should also be incorporated in the GS [89]. In addition to reporting of the carcinoma features for each biopsy, an overall (or global) GS based on the carcinoma-positive biopsies can be provided. The global GS takes into account the extent of each grade from all prostate biopsies. The 2014 ISUP endorsed grading system limits the number of PCa grades, ranging them from 1 to 5 (see Table 4.2) [88, 90].

Further sub-stratification of the intermediate-risk group can be made and specifically the National Cancer Center Network (NCCN) Guidelines subdivide intermediate-risk disease into favourable intermediate-risk and unfavourable intermediate-risk, with unfavourable features including ISUP grade 3, and/or ≥ 50% positive biopsy cores and/or at least two intermediate-risk factors [91].

Table 4.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

Table 4.3: International Society of Urological Pathology 2014 grade (group) system

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

4.3 Clinically significant prostate cancer

The descriptor ‘clinically significant’ is widely used to differentiate PCa that may cause morbidity or death from types of PCa that do not. This distinction is particularly important as insignificant PCa that does not cause harm is so common [11]. Unless this distinction is made, such cancers are at high risk of being overtreated, with the treatment itself risking harmful side effects to patients. The over-treatment of insignificant PCas has been criticised as a major drawback of PSA testing [92].

However, defining what is clinically significant and what is insignificant PCa is difficult. In large studies of RP specimens which showed only ISUP grade 1 disease, extraprostatic extension (EPE) was extremely rare (0.28% of 2,502 cases) and seminal vesicle (SV) invasion or lymph node (LN) metastasis did not occur at all [93, 94]. International Society for Urological Pathology grade 1 disease itself can therefore be considered clinically insignificant. Whilst ISUP grade 1 bears the hallmarks of cancer histologically, ISUP grade 1 itself does not behave in a clinically malignant fashion.

However, ISUP grade 1 is first diagnosed at biopsy and guides management decisions, not after the prostate has been removed. The current standard practice of MRI-targeted and template biopsies has reduced diagnostic inaccuracy [95], however sampling error may still occur such that higher grade cancer could be missed. This should be especially considered if the prior MRI showed a suspicious lesion, but only ISUP grade 1 was found at biopsy.

Another complexity in defining insignificant cancer is that ISUP grade 1 may progress to higher grades over time, becoming clinically significant at a later biopsy [96].

Therefore, although ISUP grade 1 itself can be described as clinically insignificant, it is important to take into account other factors, including imaging prior to biopsy and adequate sampling core number. When combined with low-risk clinical factors (see Table 4.2), ISUP grade 1 represents low-risk PCa, with its recommendation of preferred management being active surveillance (AS) or watchful waiting (WW) (see Sections 6.1.1.2 & 6.1.1.3). It should be noted, therefore, that defining ISUP grade 1 as insignificant cancer does not mean it should be ignored, but safely observed.

Epidemiological and autopsy data also suggest that a proportion of ISUP grade 2 PCas would remain undetectable during a man's life [97] and therefore may be overtreated. In current guidelines deferred treatment may be offered to select patients with intermediate-risk PCa [91], but evidence is lacking for appropriate selection criteria [98].

Recent papers have defined clinically significant cancer differently, commonly using ISUP grade 2 and above and even ISUP grade 3 and above, demonstrating the lack of consensus and evolution of its definition [99-102]. Some papers even provide more than one definition within a single study [103, 104]. Although there is insufficient evidence to define clearly what clinically significant (cs)PCa is, it is imperative that authors define and state it in their own studies, including exactly how the disease was diagnosed.

4.4 Prognostic relevance of stratification

A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management [105, 106]. However, as yet, the best stratification and optimal treatment remain controversial.

4.5 Guidelines for classification and staging systems

Recommendations	Strength rating
Use the Tumour, Node, Metastasis (TNM) classification for staging of PCa.	Strong
Use the International Society of Urological Pathology (ISUP) 2014 system for grading of PCa.	Strong

5. DIAGNOSTIC EVALUATION

5.1 Screening and early detection

5.1.1 Screening

Population or mass screening is defined as the 'systematic examination of asymptomatic men to identify individuals 'at risk' and is usually initiated by health authorities. The co-primary objectives are:

- reduction in mortality due to PCa;
- a maintained QoL as expressed by QoL-adjusted gain in life years (QALYs).

Prostate cancer mortality trends range widely from country to country in the industrialised world [107]. Mortality due to PCa has decreased in most Western nations but the magnitude of the reduction varies between countries. Currently, screening for PCa still remains one of the most controversial topics in the urological literature [108].

Initial widespread aggressive screening in USA was associated with a decrease in mortality [109]. In 2012 the US Preventive Services Task Force (USPSTF) released a recommendation against PSA-based screening [92], which was adopted in the 2013 AUA Guidelines [110] and resulted in a reduction in the use of PSA for early detection [111]. This reduction in the use of PSA testing was associated with higher rates of advanced disease at diagnosis (e.g., a 6% increase in the number of patients with metastatic PCa) [13, 112-115]. While PCa mortality had decreased for two decades since the introduction of PSA testing [116], the incidence of advanced disease and, possibly, cancer-related mortality slowly increased from 2008 and accelerated in 2012 [117]. Moreover, additional evidence suggests a long-term benefit of PSA population screening in terms of reduction of cancer-specific mortality [118, 119]. However, the temporal relationship between PSA testing and decreased mortality, as well as a rising mortality following immediately after the USPSTF and AUA Guidelines recommendation against PSA testing questions the direct causative link between both points.

In 2017 the USPSTF issued an updated statement suggesting that men aged 55–69 should be informed about the benefits and harms of PSA-based screening as this might be associated with a small survival benefit. The USPSTF has now upgraded this recommendation to a grade C [120], from a previous grade 'D' [120-122]. They highlighted the fact that the decision to be screened should be an individual one. The grade D recommendation remains in place for men over 70 years old. This represents a major switch from discouraging PSA-based screening (grade D) to offering early diagnosis to selected men depending on individual circumstances.

A comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction in the systematic screening group compared to a higher over-diagnosis with a marginal survival benefit, at best, in the opportunistic screening regimen [123].

A Cochrane review published in 2013 [124], which has since been updated [125], presents the main overview to date. The findings of the updated publication (based on a literature search until April 3, 2013) are almost identical to the 2009 review:

- Screening is associated with an increased diagnosis of PCa (RR: 1.3, 95% CI: 1.02–1.65).
- Screening is associated with detection of more localised disease (RR: 1.79, 95% CI: 1.19–2.70) and less advanced PCa (T3–4, N1, M1) (RR: 0.80, 95% CI: 0.73–0.87).
- From the results of 5 RCTs, randomising more than 341,000 men, no PCa-specific survival benefit was observed (RR: 1.00, 95% CI: 0.86–1.17). This was the main endpoint in all trials.
- From the results of four available RCTs, no overall survival (OS) benefit was observed (RR: 1.00, 95% CI: 0.96–1.03).

The included studies applied a range of different screening measures and testing intervals in patients who had undergone prior PSA testing, to various degrees. None included the use of risk calculators, MRI prior to biopsy (vs. a single PSA threshold) or AS (as an alternative to RP) which no longer reflects current standard practice.

The diagnostic tool (i.e. biopsy procedure) was not associated with increased mortality within 120 days after biopsy in screened men as compared to controls in the two largest population-based screening populations (ERSPC and PLCO), in contrast to a 120-day mortality rate of 1.3% in screened vs. 0.3% in controls, respectively, in a Canadian population-based screening study [126]. Increased diagnosis has historically led to over-treatment with associated side effects. However, despite this, the impact on the patient's overall QoL is still unclear. Population level screening has never been shown to be detrimental [127-129]. Nevertheless, all these findings have led to strong advice against systematic population-based screening in most countries, including those in Europe.

In case screening is considered, a single PSA test is not enough based on the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial. The CAP trial evaluated a single PSA screening vs. controls not undergoing PSA screening on PCa detection in men aged 50 to 69 years old. The single PSA screening intervention detected more low-risk PCa cases but had no significant effect on PCa mortality after a median follow-up of 10 years [130].

Since 2013, the European Randomized Study of Screening for Prostate Cancer (ERSPC) data have been updated with 16 years of follow-up (see Table 5.1) [131]. The key message is that with extended follow-up, the mortality reduction remains unchanged (21%, and 29% after non-compliance adjustment). However the number needed to screen (NNS) and to treat is decreasing, and is now below the NNS observed in breast cancer trials [131, 132]. Long-term follow-up of the PLCO (Prostate, Lung, Colon, Ovarian cancer screening trial) showed no survival benefit for screening at a median follow-up of 16.7 years but a significant 17% increase in Gleason score 2–6 cancers and 11% decrease in Gleason score 8–10 cancers [133].

Table 5.1: Follow-up data from the ERSPC study [131]

Years of follow-up	Number needed to screen	Number needed to treat
9	1,410	48
11	979	35
13	781	27
16	570	18

Most screening trials include PSA and prostate biopsies to screen for PCa. Data on screening trials incorporating MRI are emerging. The role of MRI in PSA screening was studied in two RCTs. The STHLM3 trial randomised men with a PSA > 3 ng/mL between standard biopsies (10–12 cores) or MRI and standard plus targeted biopsies in the presence of a suspicious MRI. The percentage of men that underwent prostate

biopsies in the standard group was double that of the MRI group. In this non-inferiority trial, the intention-to-treat (ITT) analysis found 18% and 21% clinically significant (ISUP > 1) disease and 12% and 4% insignificant disease in the standard and the MRI group, respectively [134]. The second trial, the IP1-PROSTAGRAM study (PSA > 3 ng/mL; MRI Prostate Imaging – Reporting and Data System (PI-RADS) > 2), showed highest detection of csPCa for MRI compared to transrectal ultrasound-guided prostate (TRUS) biopsy [135].

The integration of MRI in the biopsy protocol may reduce the number of men that undergo biopsies while detecting more clinically significant and less clinically insignificant PCa [134, 135].

Currently there is insufficient evidence to support systematic screening; but there is an increased interest in early individualised detection.

*5.1.2 **Early detection***

An individualised risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis. It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it [15, 136].

5.1.2.1 Risk factors

Men at elevated risk of having PCa are those > 50 years [137] or at age > 45 years with a family history of PCa (either paternal or maternal) [138] or of African descent [139, 140]. Men of African descent are more likely to be diagnosed with more advanced disease [141] and upgrade was more frequent after prostatectomy as compared to Caucasian men (49% vs. 26%) [142].

Germline mutations are associated with an increased risk of the development of aggressive PCa, i.e. *BRCA2* [143, 144]. Prostate-specific antigen screening in male *BRCA1* and *2* carriers detected more significant cancers at a younger age compared to non-mutation carriers [32, 33].

Men with a baseline PSA < 1 ng/mL at 40 years and < 2 ng/mL at 60 years are at decreased risk of PCa metastasis or death from PCa several decades later [145, 146].

5.1.2.2 Initial risk assessment by PSA and DRE

Informed men requesting an early diagnosis should be given a PSA test and undergo a DRE [147]. The use of DRE alone in the primary care setting had a sensitivity and specificity below 60%, possibly due to inexperience, and can therefore not be recommended to exclude PCa [148].

Prostate-specific antigen measurement and DRE need to be repeated [130], but the optimal intervals for PSA testing and DRE follow-up are unknown as they varied between several prospective trials. A risk-adapted strategy might be a consideration, based on the initial PSA level. This could be every 2 years for those initially at risk, or postponed up to 8 years in those not at risk with an initial PSA < 1 ng/mL at 40 years and a PSA < 2 ng/mL at 60 years of age and a negative family history [149]. An analysis of ERSPC data supports a recommendation for an 8-year screening interval in men with an initial PSA concentration < 1 µg/L; fewer than 1% of men with an initial PSA concentration < 1 ng/mL were found to have a concentration above the biopsy threshold of 3 ng/mL at 4-year follow-up; the cancer detection rate by 8 years was close to 1% [150]. The long-term survival and QoL benefits of extended PSA re-testing (every 8 years) remain to be proven at a population level.

5.1.2.3 Risk assessment, co-morbidity and life-expectancy

Data from the Goteborg arm of the ERSPC trial suggest that the age at which early diagnosis should be stopped remains controversial, but an individual's life expectancy must definitely be taken into account. Men who have less than a 15-year life expectancy are unlikely to benefit, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the ERSPC trials. Furthermore, although there is no simple tool to evaluate individual life expectancy; co-morbidity is at least as important as age. A detailed review can be found in Section 5.4 'Estimating life expectancy and health status' and in the SIOG Guidelines [151].

5.1.2.4 Risk assessment to determine the need for biopsy

Multiple diagnostic tools are now available to determine the need for a biopsy to establish the diagnosis of a PCa.

Risk calculators, combining clinical data (age, DRE findings, PSA level, etc.) may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available including (among others):

- the ERSPC cohort: http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators; An updated version was presented in 2017 including prediction of low and high risk now also based on the ISUP grading system and presence of cribriform growth in histology [152];
- the PCPT cohort: PCPTRC 2.0 http://myprostatecancerrisk.com/;
- a local Canadian cohort: https://sunnybrook.ca/content/?page=asure-calc (among others).

Prostate MRI stratifies suspected PCa in lower- and higher risk, based on a 1- to 5- risk scale of having csPCa [PI-RADS v2.1 guidelines 2019]. A recent meta-analysis of this risk assessment tool showed (on a patient level) a significant cancer detection rate of 9% (5–13%) for PI-RADS 2 scores, 16% (7–27%) for PI-RADS 3 scores, 59% (39–78%) for PI-RADS 4 scores, and 85% (73–94%) for PI-RADS 5 scores [153]. Men with PI-RADS assessment scores of 3 to 5 are recommended to undergo biopsy [154]. Prostate MRI and related MRI-directed biopsies have shown to be at least as diagnostically effective as systematic biopsies alone in diagnosing significant cancers [155]. However, if the MRI-directed biopsy decision strategy (without performing systematic biopsies) can reduce the number of unnecessary biopsy procedures, this will be at the expense of missing a small percentage of csPCas [156] (see Section 5.2.4.2.4).

PSA-density (PSA-D) is the strongest predictor in risk calculators. Combinations of PSA-D and MRI have been explored [157-162], showing guidance in biopsy-decisions whilst safely avoiding redundant biopsy testing (see Section 5.2.4.2.6.3).

Urine and serum biomarkers as well as tissue-based biomarkers have been proposed for improving detection and risk stratification of PCa patients, potentially avoiding unnecessary biopsies. However, further studies are necessary to validate their efficacy [163]. At present there is too limited data to implement these markers into routine screening programmes (see Section 5.2.3).

*5.1.3 **Genetic testing for inherited prostate cancer***

Increasing evidence supports the implementation of genetic counselling and germline testing in early detection and PCa management [164]. Several commercial screening panels are now available to assess main PCa risk genes [165]. However, it remains unclear when germline testing should be considered and how this may impact localised and metastatic disease management. Germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population [166]. It is important to understand the difference between somatic testing, which is performed on the tumour, and germline testing, which is performed on blood or saliva and identifies inherited mutations. Genetic counselling is required prior to and after undergoing germline testing.

Germline mutations can drive the development of aggressive PCa. Therefore, the following men with a personal or family history of PCa or other cancer types arising from DNA repair gene mutations should be considered for germline testing:

- Men with metastatic PCa;
- Men with high-risk PCa and a family member diagnosed with PCa at age < 60 years;
- Men with multiple family members diagnosed with csPCa at age < 60 years or a family member who died from PCa cancer;
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

Further research in this field (including not so well-known germline mutations) is needed to develop screening, early detection and treatment paradigms for mutation carriers and family members.

Table 5.2: Germline mutations in DNA repair genes associated with increased risk of prostate cancer

Gene	Location	Prostate Cancer risk	Findings
BRCA2	13q12.3	- 2.5 to 4.6 [167, 168] - PCa at 55 years or under: RR: 8–23 [167, 169]	• up to 12 % of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA2* [5.3%]) [25] • 2% of men with early-onset PCa harbour germline mutations in the *BRCA2* gene [167] • *BRCA2* germline alteration is an independent predictor of metastases and worse PCa-specific survival [29, 170]

ATM	11q22.3	RR: 6.3 for metastatic prostate [25]	• higher rates of lethal PCa among mutation carriers [31] • up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *ATM* [1.6%]) [25]
CHEK2	22q12.1	OR 3.3 [171, 172]	• up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *CHEK2* [1.9%]) [25]
BRCA1	17q21	RR: 1.8–3.8 at 65 years or under [173, 173]	• higher rates of lethal PCa among mutation carriers [31] • up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA1* [0.9%]) [25]
HOXB13	17q21.2	OR 3.4–7.9 [26, 175]	• significantly higher PSA at diagnosis, higher Gleason score and higher incidence of positive surgical margins in the RP specimen than non-carriers [176]
MMR genes *MLH1* *MSH2* *MSH6* *PMS2*	3p21.3 2p21 2p16 7p22.2	RR: 3.7 [177]	• mutations in *MMR* genes are responsible for Lynch syndrome [146] • *MSH2* mutation carriers are more likely to develop PCa than other *MMR* gene mutation carriers [178]

BRCA2 = breast cancer gene 2; ATM = ataxia telangiectasia mutated; CHEK2 = checkpoint kinase 2; BRCA1 = breast cancer gene 1; HOXB13 = homeobox B13; MMR = mismatch repair; MLH1 = mutL homolog 1; MSH2 = mutS homolog 2; MSH6 = mutS homolog 6; OR = odds ratio; PMS2 = post-meiotic segregation increased 2; PCa = prostate cancer; RR = relative risk.

*5.1.4 **Guidelines for germline testing****

Recommendations	Strength rating
Consider germline testing in men with metastatic PCa.	Weak
Consider germline testing in men with high-risk PCa who have a family member diagnosed with PCa at age < 60 years.	Weak
Consider germline testing in men with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa.	Weak
Consider germline testing in men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Weak

**Genetic counseling is required prior to germline testing.*

*5.1.5 **Guidelines for screening and early detection***

Recommendations	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man and a life-expectancy of at least 10 to 15 years.	Weak
Offer early PSA testing to well-informed men at elevated risk of having PCa: • men from 50 years of age; • men from 45 years of age and a family history of PCa; • men of African descent from 45 years of age; • men carrying *BRCA2* mutations from 40 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age; Postpone follow-up to 8 years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

5.2 Clinical diagnosis

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores.

5.2.1 *Digital rectal examination*

In ~18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [179]. A suspect DRE in patients with a PSA level ≤ 2 ng/mL has a positive predictive value (PPV) of 5–30% [180]. In the ERSPC trial, an abnormal DRE in conjunction with an elevated PSA more than doubled the risk of a positive biopsy (48.6% vs. 22.4%) [181]. An abnormal DRE is associated with an increased risk of a higher ISUP grade, predicts csPCa in men under AS [182] and is an indication for MRI and biopsy [181, 183]. cT staging is dependent on DRE and a strong predictor of advanced PCa (OR: 11.12 for cT3 and OR: 5.28 for cT4) [184].

5.2.2 *Prostate-specific antigen*

The use of PSA as a serum marker has revolutionised PCa diagnosis [185]. Prostate-specific antigen is organ- but not cancer specific; therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. As an independent variable, PSA is a better predictor of cancer than either DRE or TRUS [186].

There are no agreed standards defined for measuring PSA [187]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Many men may harbour PCa despite having low serum PSA [188]. Table 5.3 demonstrates the occurrence of ISUP ≥ grade 2 PCa in systematic biopsies at low PSA levels, precluding an optimal PSA threshold for detecting non-palpable but csPCa. The use of nomograms and biomarkers may help in predicting indolent PCa [134, 189, 190]. In case of an elevated PSA (up to 10 ng/mL), a repeated test should considered to confirm the increase before going to the next step.

5.2.2.1 *Repeat PSA testing*

A repeat PSA test before prostate biopsies in men with an initial PSA 3–10 ng/mL reduced the indication for biopsies in 16.8% of men while missing 5.4% ISUP grade > 1 in the STHLM3 trial [191]. Similarly, in the Prostate Testing for Cancer and Treatment (ProtecT) trial men with a more than 20% lower repeat-PSA analysis within 7 weeks had a lower risk of PCa (OR: 0.43, 95% CI: 0.35–0.52) as well as a lower risk of ISUP grade ≥ 2 (OR: 0.29, 95% CI: 0.19–0.44) [192]. A study with a PSA interval of 4 weeks showed similar findings of a reduced risk of PCa and ISUP grade > 1 [193]. These observations indicate that an early repeat-PSA prior to the decision of prostate biopsies has prognostic information.

Table 5.3: Risk of PCa identified by systemic PCa biopsy in relation to low PSA values [160]

PSA level (ng/mL)	Risk of PCa (%)	Risk of ISUP grade ≥ 2 PCa (%)
0.0–0.5	6.6	0.8
0.6–1.0	10.1	1.0
1.1–2.0	17.0	2.0
2.1–3.0	23.9	4.6
3.1–4.0	26.9	6.7

5.2.2.2 *PSA density*

Prostate-specific antigen density is the level of serum PSA divided by the prostate volume. The higher the PSA-D, the more likely it is that the PCa is clinically significant; in particular in smaller prostates when a PSA-D cut-off of 0.15 ng/mL/cc was applied [194] (see Section 5.2.4.2.6.3). Several studies found a PSA-D over 0.1–0.15 ng/mL/cc predictive of cancer [195, 196]. Patients with a PSA-D below 0.09 ng/mL/cc were found unlikely (4%) to be diagnosed with csPCa [197]. A systematic review showed heterogeneity among studies using PSA-D to select men with PI-RADS 3 category on MRI reading for biopsies but suggest a cut-off of 0.15 ng/mL/cc [195]. Others found its added value to biparametric (bp) MRI-guided biopsies unclear with an area under the curve (AUC) of 0.87–0.95 for the direction of csPCa based on bpMRI and 0.91–0.95 for the combined test of bpMRI and PSA-D [198].

5.2.2.3 *PSA velocity and doubling time*

Various PSA kinetics definitions have been proposed with different methods of calculation (log transformed or not) and eligible PSAs:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year) [199];
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time [200].

Prostate-specific antigen velocity is more simple to calculate by subtracting the initial value from the final value, dividing by time. However, by ignoring middle values, not all PSA values are accurately taken into account.

Prostate-specific antigen-DT is calculated assuming an exponential rise in serum PSA. The formula takes into account the natural logarithm of 2 divided by the slope obtained from fitting a linear regression of the natural log of PSA over time [201]. However, many different PSA-DT calculations have been assessed according to the mathematical formula used and to the included PSA values (number, time period, intervals) [202]. For example, the 'MSKCC' method calculates a regression slope integrating all PSA values. Other methods transform PSA before calculating the slope and do not include all PSA values (different time frames and minimal intervals) [203]. Thus, O'Brien and colleagues identified more than 20 different definitions of PSAV and PSA-DT and demonstrated that obtained values could vary widely between definitions [203].

However, some rules can be considered for PSA-DT calculation:

- At least 3 PSA measurements are required [201];
- A minimum time period between measurements (4 weeks) is preferable due to potential statistical 'noise' when PSA values are obtained too close together (this statement can be reconsidered in case of very active disease);
- All PSA values should be ≥ 0.20 ng/mL and follow a global rising trend;
- All included PSA values should be obtained within the past 12 months at most, to reflect the current disease activity;
- PSA-DT is often mentioned in months, or in weeks in very active disease.

Prostate-specific antigen velocity and PSA-DT may have a prognostic role in treating PCa but have limited diagnostic use because of background noise (total prostate volume, and BPH), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time [201]. These measurements do not provide additional information compared with PSA alone [203-206]. Prostate-specific antigen-DT has been linked with metastasis-free- and OS in non-metastatic CRPC (nmCRPC) and identifies patients with high-risk nmCRPC who could benefit from intensified therapy (PSA-DT threshold < 10 months) [207].

5.2.2.4 Free/total PSA ratio

Free/total (f/t) PSA must be used cautiously because it may be adversely affected by several pre-analytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [208]. Prostate cancer was detected in men with a PSA 4–10 ng/mL by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 ng/mL [209]. A systematic review including 14 studies found a pooled sensitivity of 70% in men with a PSA of 4–10 ng/mL [210]. Free/total PSA is of no clinical use if the total serum PSA is > 10 ng/mL or during follow-up of known PCa. The clinical value of f/t PSA is limited in light of the new diagnostic pathways incorporating MRI (see Section 5.2.4.2).

*5.2.3 **Biomarkers***

5.2.3.1 Blood based biomarkers: PHI/4K score/IsoPSA

Several assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the U.S. Food and Drug Administration (FDA) approved Prostate Health Index (PHI) test (combining free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2] in addition to age, DRE and prior biopsy status). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. A few prospective multi-centre studies demonstrated that both the PHI and 4K score test out-performed f/t PSA PCa detection, with an improved prediction of csPCa in men with a PSA between 2–10 ng/mL [211-214]. In a head-to-head comparison both tests performed equally [215].

In contrast to the 4K score and PHI, which focus on the concentration of PSA isoforms, IsoPSA utilises a novel technology which focuses on the structure of PSA [216]. Using an aqueous two-phase solution, it partitions the isoforms of PSA and assesses for structural changes in PSA. In a multi-centre prospective validation in 271 men the assay AUC was 0.784 for high-grade vs. low-grade cancer/benign histology, which was superior to the AUCs of total PSA and percent free PSA [217]. In men with a negative mpMRI, PSA-D, 4K score and family history predicted the risk of csPCa on biopsy and using a nomogram reduced the number of negative biopsies and indolent cancers by 47% and 15%, respectively, while missing 10% of csPCas [218].

The Stockholm3 test is a prediction model that is based on several clinical variables (age, first-degree family history of PCa, and previous biopsy), blood biomarkers (total PSA, free PSA, ratio of free PSA to total PSA, human kallikrein 2, macrophage inhibitory cytokine-1, and *microseminoprotein-β [MSMB]*), and a polygenic risk score for predicting the risk of PCa with ISUP ≥ 2, and was shown to reduce the percent of clinically insignificant cancers when used on combination of MRI in a PSA screening population [134].

5.2.3.2 *Urine biomarkers: PCA3/SelectMDX/Mi Prostate score (MiPS)/ExoDX*

Prostate cancer gene 3 (*PCA3*) is an overexpressed long non-coding RNA (lncRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available Progensa urine test for *PCA3* is superior to total and percent-free PSA for the detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve (AUC) for positive biopsies [219-222]. *PCA3* score increases with PCa volume, but there are conflicting data about whether it independently predicts the ISUP grade [223]. Currently, the main indication for the Progensa test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain [224]. Wei *et al.*, showed 42% sensitivity at a cut-off of 60 in the primary biopsy setting with a high specificity (91%) and a PPV of 80% suggesting that the assay may be used in the primary setting [225].

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of *HOXC6* and *DLX1* mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer [226]. A multi-centre trial evalutated SelectMDX in men with a MRI PI-RADS score < 4 or PI-RADS score < 3, and the percentage of missed csPCas was 6.5% and 3.2%, respectively, whereas 45.8% and 40% of biopsies were avoided [227]. Hendriks *et al.*, found more biopsies were avoided and more high-grade PCas detected in a MRI-based biopsy strategy compared to a SelectMDX strategy. When both tests were combined, more GG > 1 lesions were found, but the number of negative or low-grade cancer biopsies more than doubled [190]. Combining SelectMDX and MRI in men with a PSA between 3–10 ng/mL had a negative predictive value (NPV) of 93% [228]

TMPRSS2-ERG fusion, a fusion of the trans-membrane protease serine 2 (*TMPRSS2*) and the *ERG* gene can be detected in 50% of PCas [229]. When detection of *TMPRSS2-ERG* in urine was added to *PCA3* expression and serum PSA (Mi(chigan)Prostate Score [MiPS]), cancer prediction improved [230]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [231, 232]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care (SOC). However, currently, both the MiPS-score and ExoDx assay are considered investigational.

In 6 head-to-head comparison studies of *PCA3* and PHI, only Seisen *et al.*, found a significant difference; *PCA3* detected more cancers, but for the detection of significant disease, defined as ISUP grade ≥ 2, more than three positive cores, or > 50% cancer involvement in any core, PHI proved superior [233]. Russo *et al.*, suggested in their systematic review that, based on moderate quality data, PHI and the 4K panel had a high diagnostic accuracy and showed similar performance in predicting the detection of significant disease with an AUC of 0.82 and 0.81, respectively [234]. However, in the screening population of the ERSPC study the use of both *PCA3* and 4K panel when added to the risk calculator led to an improvement in AUC of less than 0.03 [235]. Based on the available evidence, some biomarkers could help in discriminating between aggressive and non-aggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians [236]. However, upfront MRI is also likely to affect the utility of above-mentioned biomarkers (see Section 5.2.4).

5.2.3.3 *Biomarkers to select men for a repeat biopsy*

In men with an elevated risk of PCa with a prior negative biopsy, additional information may be gained by the Progensa-*PCA3* and SelectMDX DRE urine tests, the serum 4Kscore and PHI tests or a tissue-based epigenetic test (ConfirmMDx). The role of PHI, Progensa *PCA3*, and SelectMDX in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective [224]. The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. In case PCa is missed at biopsy, demonstration of epigenetic changes in the benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes (Methylated *APC, RASSF1* and *GSTP1*) in benign prostatic tissue. A multi-centre study found a NPV of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men [237]. Given the limited available data and the fact that the role of MRI in tumour detection was not accounted for, no recommendation can be made regarding the routine application of ConfirmMDX, in particular in the light of current use of MRI before biopsy.

5.2.3.4 *Guidelines for risk-assessment of asymptomatic men*

Recommendations	Strength rating
In asymptomatic men with a prostate-specific antigen (PSA) level between 3–10 ng/mL and a normal digital rectal examination (DRE), repeat the PSA test prior to further investigations.	Weak

In asymptomatic men with a PSA level between 2–10 ng/mL and a normal DRE, use one of the following tools for biopsy indication: • risk-calculator; • Magnetic resonance imaging of the prostate	Strong
• an additional serum, urine or tissue-based biomarker test.	Weak

*5.2.4 **Imaging***

5.2.4.1 Transrectal ultrasound and ultrasound-based techniques

Standard TRUS is not reliable at detecting PCa [238] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [100]. Prostate HistoScanning™ provided inconsistent results across studies [239]. New sonographic modalities such as micro-Doppler, sonoelastography contrast-enhanced US or high-resolution micro-US provided promising preliminary findings, either alone, or combined into the so-called 'multiparametric US'. However, these techniques still have limited clinical applicability due to lack of standardisation, lack of large-scale evaluation of inter-reader variability and unclear results in transition zones [240-242].

5.2.4.2 Magnetic resonance imaging

5.2.4.2.1 Magnetic resonance imaging performance in detecting PCa

Correlation with RP specimens shows that MRI has good sensitivity for the detection and localisation of ISUP grade ≥ 2 cancers, especially when their diameter is larger than 10 mm [243-245]. This good sensitivity was further confirmed in patients who underwent template biopsies. In a Cochrane meta-analysis which compared MRI to template biopsies (≥ 20 cores) in biopsy-naive and repeat-biopsy settings, MRI had a pooled sensitivity of 0.91 (95% CI: 0.83–0.95) and a pooled specificity of 0.37 (95% CI: 0.29–0.46) for ISUP grade ≥ 2 cancers [155]. For ISUP grade ≥ 3 cancers, MRI pooled sensitivity and specificity were 0.95 (95% CI: 0.87–0.99) and 0.35 (95% CI: 0.26–0.46), respectively. Magnetic resonance imaging is less sensitive in identifying ISUP grade 1 PCa. It identifies less than 30% of ISUP grade 1 cancers smaller than 0.5 cc identified on RP specimens by histopathology analysis [243]. In series using template biopsy findings as the reference standard, MRI has a pooled sensitivity of 0.70 (95% CI: 0.59–0.80) and a pooled specificity of 0.27 (95% CI: 0.19–0.37) for identifying ISUP grade 1 cancers [155].

The probability of detecting malignancy by MRI-identified lesions was standardised first by the use of a 5-grade Likert score [246], and then by the PI-RADS score which has been updated several times since its introduction [247, 248]. In a meta-analysis of 17 studies involving men with suspected or biopsy-proven PCa, the average PPVs for ISUP grade ≥ 2 cancers of lesions with a PI-RADSv2.1 score of 3, 4 and 5 were 16% (7–27%), 59% (39–78%), and 85% (73–94%), respectively, but with significant heterogeneity among studies [249].

5.2.4.2.2 Targeted biopsy improves the detection of ISUP grade ≥ 2 cancer as compared to systematic biopsy.

In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy (median number of cores: 8–15) and MRI-targeted biopsies (median number of cores: 2–7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02–1.23) for ISUP grade ≥ 2 cancers and 1.20 (95% CI: 1.06–1.36) for ISUP grade ≥ 3 cancers, and therefore in favour of MRI-targeted biopsy.

Another meta-analysis of RCTs limited to biopsy-naive patients with a positive MRI found that MRI-targeted biopsy detected significantly more ISUP grade ≥ 2 cancers than systematic biopsy (risk difference, -0.11 [95% CI: -0.2 to 0.0]; p = 0.05), in prospective cohort studies (risk difference, -0.18 [95% CI: -0.24 to -0.11]; p < 0.00001), and in retrospective cohort studies (risk difference, -0.07 [95% CI: -0.12 to -0.02]; p = 0.004).

Three prospective multi-centre trials evaluated MRI-targeted biopsy in biopsy-naive patients. In the Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION) trial, 500 biopsy-naive patients were randomised to either MRI-targeted biopsy only or TRUS-guided systematic biopsy only. The detection rate of ISUP grade ≥ 2 cancers was significantly higher in men assigned to MRI-targeted biopsy (38%) than in those assigned to systemic biopsy (26%, p = 0.005, detection ratio 1.46) [99]. In the Assessment of Prostate MRI Before Prostate Biopsies (MRI-FIRST) trial, 251 biopsy-naive patients underwent TRUS-guided systematic biopsy by an operator who was blinded to MRI findings, and MRI-targeted biopsy by another operator. Magnetic resonance Imaging-targeted biopsy detected ISUP grade ≥ 2 cancers in a higher percentage of patients but the difference was not significant (32.3% vs. 29.9%, p = 0.38; detection ratio: 1.08) [100]. However, MRI-targeted biopsy detected significantly more ISUP grade ≥ 3 cancers than systematic biopsy (19.9% vs. 15.1%, p = 0.0095; detection ratio: 1.32). A similar trend for improved detection of ISUP grade ≥ 3 cancers by MRI-targeted biopsy was observed in the Cochrane analysis; however, it was not statistically significant (detection ratio 1.11 [0.88–1.40]) [155]. The Met Prostaat MRI Meer Mans (4M) study included 626 biopsy-naive patients; all patients underwent systematic biopsy, and those with a positive MRI (PI-RADSv2 score of 3–5, 51%) underwent additional in-bore MRI-targeted biopsy. The results were close to those of the MRI-FIRST trial with a detection ratio for ISUP grade ≥ 2 cancers of 1.09 (detection rate: 25% for

MRI-targeted biopsy vs. 23% for systematic biopsy) [101]. However, in this study, MRI-targeted biopsy and systematic biopsy detected an equal number of ISUP grade ≥ 3 cancers (11% vs. 12%; detection ratio: 0.92).

The Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies (FUTURE) randomised trial compared three techniques of MRI-targeted biopsy in the repeat-biopsy setting [250]. In the subgroup of 152 patients who underwent both MRI-targeted biopsy and systematic biopsy, MRI-targeted biopsy detected significantly more ISUP grade ≥ 2 cancers than systematic biopsy (34% vs. 16%; p < 0.001, detection ratio of 2.1), which is a finding consistent with the Cochrane agreement analysis (detection ratio: 1.44). An ISUP grade ≥ 2 cancer would have been missed in only 1.3% (2/152) of patients, had systematic biopsy been omitted [251]. These findings support that MRI-targeted biopsy significantly out-performs systematic biopsy for the detection of ISUP grade ≥ 2 in the repeat-biopsy setting. In biopsy-naive patients, the difference appears to be less marked but remains in favour of MRI-targeted biopsy.

5.2.4.2.3 MRI-targeted biopsy without systematic biopsy reduces the detection of ISUP grade 1 PCa as compared to systematic biopsy

In pooled data of 25 head-to-head comparisons between systematic biopsy and MRI-targeted biopsy, the detection ratio for ISUP grade 1 cancers was 0.62 (95% CI: 0.44–0.88) in patients with prior negative biopsy and 0.63 (95% CI: 0.54–0.74) in biopsy-naive patients [155]. In the PRECISION and 4M trials, the detection rate of ISUP grade 1 patients was significantly lower in the MRI-targeted biopsy group as compared to systematic biopsy (9% vs. 22%, p < 0.001, detection ratio of 0.41 for PRECISION; 14% vs. 25%, p < 0.001, detection ratio of 0.56 for 4M) [99, 101]. In the MRI-FIRST trial, MRI-targeted biopsy detected significantly fewer patients with clinically insignificant PCa (defined as ISUP grade 1 and maximum cancer core length < 6 mm) than systematic biopsy (5.6% vs. 19.5%, p < 0.0001, detection ratio of 0.29) [100]. Consequently, MRI-targeted biopsy without systematic biopsy significantly reduces over-diagnosis of low-risk disease, as compared to systematic biopsy.

5.2.4.2.4 Added value combining systematic biopsy and targeted biopsy

Magnetic resonance imaging-targeted biopsies can be used in two different diagnostic pathways: 1) the 'combined pathway', in which patients with a positive MRI undergo combined systematic and targeted biopsy, and patients with a negative MRI undergo systematic biopsy; 2) the 'MRI pathway', in which patients with a positive MRI undergo only MRI-targeted biopsy, and patients with a negative MRI who are not biopsied at all.

Data from the Cochrane meta-analysis and from the MRI-FIRST and 4M trials suggest that the absolute added value of systemic biopsy for detecting ISUP grade ≥ 2 cancers is lower than that of MRI-targeted biopsy (see Table 5.4).

Table 5.4: Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 cancer detection

		ISUP ≥ 2			**ISUP ≥ 3**		
ISUP grade		**Cochrane meta-analysis*** [155]	**MRI-FIRST trial*** [100]	**4M trial** [101]	**Cochrane meta-analysis*** [155]	**MRI-FIRST trial*** [100]	**4M trial** [101]
Biopsy-naïve	Added value of MRI-TBx	6.3% (4.8–8.2)	7.6% (4.6–11.6)	7.0% (ND)	4.7% (3.5–6.3)	6.0% (3.4–9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6–6.9)	5.2% (2.8–8.7)	5.0% (ND)	2.8% (1.7–4.8)	1.2% (0.2–3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7–32.6)	37.5% (31.4–43.8)	30% (ND)	15.5% (12.6–19.5)	21.1% (16.2–26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7–11.8)	-	-	6.3% (5.2–7.7)	-	-
	Added value of systematic biopsy	2.3% (1.2–4.5)	-	-	1.1% (0.5–2.6)	-	-
	Overall prevalence	22.8% (20.0–26.2)	-	-	12.6% (10.5–15.6)	-	-

**Intervals in parenthesis are 95% CI.*

The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.

ISUP = International Society for Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

In Table 5.4, the absolute added values refer to the percentage of patients in the entire cohort; if the cancer prevalence is taken into account, the 'relative' percentage of additional detected PCa can be computed. Adding MRI-targeted biopsy to systematic biopsy in biopsy-naive patients increases the number of ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-targeted biopsy increases detection of ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naive patients would miss approximately 16% of all detected ISUP grade ≥ 2 PCa and 18% of all ISUP grade ≥ 3 PCa. In the repeat-biopsy setting, it would miss approximately 10% of ISUP grade ≥ 2 PCa and 9% of ISUP grade ≥ 3 PCa.

5.2.4.2.5 Avoiding biopsies in the 'MR pathway'

The diagnostic yield and number of biopsy procedures potentially avoided by the 'MR pathway' depends on the Likert/PI-RADS threshold used to define a positive MRI. In pooled studies on biopsy-naive patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of ≥ 3 would have avoided 30% (95% CI: 23–38) of all biopsy procedures while missing 11% (95% CI: 6–18) of all detected ISUP grade ≥ 2 cancers (relative percentage) [155]. Increasing the threshold to ≥ 4 would have avoided 59% (95% CI: 43–78) of all biopsy procedures while missing 28% (95% CI: 14–48) of all detected ISUP grade ≥ 2 cancers [155]. Of note, the percentages of negative MRI (Likert/PI-RADS score ≤ 2) in the MRI-FIRST, PRECISION and 4M trials were 21.1%, 28.9% and 49%, respectively [99-101].

5.2.4.2.6 Practical considerations

5.2.4.2.6.1 Prostate magnetic resonance imaging reproducibility

Despite the use of the PI-RADSv2 scoring system [247], MRI inter-reader reproducibility remains moderate at best which currently limits its broad use by non-dedicated radiologists [252]. However, significant improvement in the accuracy of MRI and MRI-targeted biopsy can be observed over time, both in academic and community hospitals, especially after implementation of PI-RADSv2 scoring and multidisciplinary meetings using pathological correlation and feedback [253-256]. An updated version of the PI-RADS score (PI-RADSv2.1) has been recently published to improve reader reproducibility, showing improved diagnostic performance [153] but it has not yet been fully evaluated [248]. It is still too early to predict whether quantitative approaches and computer-aided diagnostic systems will improve the characterisation of lesions seen at MRI [257]. Standardisation of MRI interpretation and quality check of acquisition and of MRI-targeted biopsy technique is required to optimise the 'MRI pathway' in large-volume and small-volume (non-expert) centres [258-260].

5.2.4.2.6.2 Targeted biopsy accuracy and reproducibility

Clinically significant PCa not detected by the 'MRI pathway' can be missed because of MRI failure (invisible cancer or reader's misinterpretation) or because of targeting failure (target missed or under sampled by MRI-targeted biopsy). In two retrospective studies of 211 and 116 patients with a unilateral MRI lesion, targeted biopsy alone detected 73.5–85.5% of all csPCa (ISUP grade ≥ 2); combining MRI-targeted biopsy with systematic biopsy of the lobe with the MRI lesion detected 96–96.4% of all csPCas and combined targeted and systematic biopsy of the contralateral lobe only identified 81.6–92.7% of csPCas [261, 262]. The difference may reflect targeting errors leading to undersampling of the tumour. The accuracy of MRI-targeted biopsy is substantially impacted by the experience of the biopsy operator [252]. Increasing the number of cores taken per target may partially compensate for guiding imprecision. In a retrospective study of 479 patients who underwent MRI-targeted biopsy with 4 cores per target that were sequentially labelled, the first 3 cores detected 95.1% of csPCa [263]. In two other retrospective studies of 330 and 744 patients who underwent MRI-targeted biopsy with up to 5 cores per target, the one-core and 3-core sampling strategies detected 63–75% and 90–93%, respectively, of the ISUP grade ≥ 2 PCas detected by the 5-core strategy [264, 265]. These percentages are likely to be influenced by the lesion size and location, the prostate volume or the operator's experience, but no study has quantified the impact of these factors yet.

5.2.4.2.6.3 Risk-stratification

Using risk-stratification to avoid biopsy procedures

Prostate-specific antigen density may help refine the risk of csPCa in patients undergoing MRI as PSA-D and the PI-RADS score are significant independent predictors of csPCa at biopsy [266, 267]. In a meta-analysis of 8 studies, pooled MRI NPV for ISUP grade ≥ 2 cancer was 84.4% (95% CI: 81.3–87.2) in the whole cohort, 82.7% (95% CI: 80.5–84.7) in biopsy-naive men and 88.2% (95% CI: 85–91.1) in men with prior negative biopsies. In the subgroup of patients with PSA-D < 0.15 ng/mL, NPV increased to respectively 90.4% (95% CI: 86.8–93.4), 88.7% (95% CI: 83.1–93.3) and 94.1% (95% CI: 90.9–96.6) [268]. In contrast, the risk of csPCa is as high as 27–40% in patients with negative MRI and PSA-D > 0.15–0.20 ng/mL/cc [101, 159, 267, 269-271].

Based on a meta-analysis of > 3,000 biopsy-naïve men, a risk-adapted data table of csPCa was developed, linking PI-RADS score (1-2, 3, and 4-5) to PSA-D categories (< 0.10, 0.10–0.15, 0.15–0.20 and > 0.20 ng/mL) (Table 5.5) [157]. For example, the risk of having ISUP grade ≥ 2 cancer in biopsy-naïve men with a PI-RADS 1–2 assessment score and PSA-D below 0.10 is 3–4%, in a below-average-risk population of < 5% [157]. This risk-adapted matrix table based on PSA-D and on MRI risk assessments may guide the decision to perform a biopsy.

These data are applicable for a mean ISUP grade ≥ 2 cancer prevalence of 35% (range 28–46%) in biopsy-naive men, and would need to be adjusted to other populations' prevalence. Awaiting validation of MRI-based multivariate risk-prediction tools, corroboration linking MRI findings to PSA-D values for biopsy decisions is beginning to emerge which may promote their routine use in clinical practice [16, 272]. It must be emphasised, however, that the use of PSA-D remains currently limited due to the lack of standardisation of prostate volume measurement (assessed by DRE or by imaging [TRUS or MRI using various techniques such as ellipsoid formula or planimetry]). The impact of this lack of standardisation on the volume estimation remains under-evaluated.

Table 5.5: Risk data table of clinically significant prostate cancer, related to PI-RADS score and PSA-D categories in biopsy-naive men, clinically suspected of having significant disease [157]*

Detection of clinically significant prostate cancer (ISUP grade 2 and higher)					
		PSA-density risk groups			
PI-RADS risk categories	Prevalence ISUP ≥ 2 PCa	Low < 0.10	Intermediate-low 0.10–015	Intermediate-high 0.15–0.20	High ≥ 0.20
		31% (678/2199)	28% (612/2199)	16% (360/2199)	25% (553/2199)
Compiled totals of csPCa risk					
PI-RADS 1–2	6% (48/839)	3% (11/411)	7% (17/256)	8% (8/104)	18% (12/68)
PI-RADS 3	16% (41/254)	4% (3/74)	13% (11/88)	29% (12/41)	29% (15/51)
PI-RADS 4–5	62% (687/1106)	31% (59/189)	54% (144/286)	69% (148/215)	77% (336/434)
All PI-RADS	35% (776/2199)	11% (73/674)	28% (172/612)	47% (168/360)	66% (363/553)
Risk-adapted matrix table for biopsy decision management					
PI-RADS 1–2		No biopsy	No biopsy	No biopsy	Consider biopsy
PI-RADS 3		No biopsy	Consider biopsy	Highly consider biopsy	Perform biopsy
PI-RADS 4–5		Perform biopsy	Perform biopsy	Perform biopsy	Perform biopsy

very low	0–5% csPCa (below population risk) #
low	5–10% csPCa (acceptable risk) ##
Intermediate-low	10–20% csPCa
Intermediate-high	20–30% csPCa
High	30–40% csPCa
Very high	> 40% csPCa

Thompson IM *et al.* N Engl J Med. 2004 May 27;350(22):2239-46. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng/ml.
2019 EAU guidelines: csPCa 9% (95%CI: 6–14%).

Table adapted from: Schoots, IG and Padhani AR. BJU Int 2021 127(2):175. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation, with permission from Wiley.

Combining MRI findings with the *PCA3* score may also improve risk stratification [273]. Several groups have developed comprehensive risk calculators which combine MRI findings with simple clinical data as a tool to predict subsequent biopsy results [274]. At external validation, they tended to outperform risk calculators not incorporating MRI findings (ERSPC and Prostate Cancer Prevention Trial) with good discriminative power (as measured by the AUC). However, they also tended to be miscalibrated with under- or over-prediction of the risk of ISUP grade ≥ 2 cancer [275, 276]. In one study that externally assessed four risk calculators combining MRI findings and clinical data, only two demonstrated a distinct net benefit when a risk of false-negative prediction of 15% was accepted. The others were harmful for this risk level, as compared to the 'biopsy all' strategy [275]. This illustrates the prevalence-dependence of risk models. Recalibrations taking into account the local prevalence are possible, but this approach is difficult in routine clinical practice as the local prevalence is difficult to estimate and may change over time.

Using risk-stratification to avoid MRI and biopsy procedures

A retrospective analysis including 200 men from a prospective database of patients who underwent MRI and combined systematic and targeted biopsy showed that upfront use of the Rotterdam Prostate Cancer Risk Calculator would have avoided MRI and biopsy in 73 men (37%). Of these 73 men, 10 had ISUP grade 1 cancer and 4 had ISUP grade ≥ 2 cancer [277]. A prospective multi-centre study evaluated several diagnostic pathways in 545 biopsy-naive men who underwent MRI and systematic and targeted biopsy. Using a PHI threshold of ≥ 30 to perform MRI and biopsy would have avoided MRI and biopsy in 25% of men at the cost of missing 8% of the ISUP grade ≥ 2 cancers [278]. Another prospective multi-centre trial including 532 men (with or without history of prostate biopsy) showed that using a threshold of ≥ 10% for the Stockholm3 test to perform MRI and biopsy would have avoided MRI and biopsy in 38% of men at the cost of missing 8% of ISUP grade ≥ 2 cancers [279].

5.2.4.2.6.4 Potential cancer grade shift, induced by improved diagnosis by MRI and MRI-targeted biopsy

Magnetic resonance imaging findings are significant predictors of adverse pathology features on prostatectomy specimens, and of survival-free BCR after RP or RT [84, 280-282]. In addition, tumours visible on MRI are enriched in molecular hallmarks of aggressivity, as compared to invisible lesions [283]. Thus, MRI does identify aggressive tumours.

Nonetheless, as MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer, ISUP grade ≥ 2 cancers detected by MRI-targeted biopsy are, on average, of better prognosis than those detected by the classical diagnostic pathway (Will Rogers phenomenon [86]). This is illustrated in a retrospective series of 1,345 patients treated by RP which showed that, in all risk groups, patients diagnosed by MRI-targeted biopsy had better BCR-free survival than those diagnosed by systematic biopsy only [84]. To mitigate this grade shift, in case of targeted biopsies, the 2019 ISUP consensus conference recommended using an aggregated ISUP grade summarizing the results of all biopsy cores from the same MR lesion, rather than using the result from the core with the highest ISUP grade [89]. When long-term follow-up of patients who underwent MRI-targeted biopsy is available, a revision of the risk-groups definition will become necessary. In the meantime, results of MRI-targeted biopsy must be interpreted in the context of this potential grade shift [284].

5.2.4.2.7 MRI and MRI-targeted biopsy results depend on the a *priori* risk of csPCa

The 'MRI pathway' is appealing since it could decrease the number of biopsy procedures, reduce the detection of low-grade PCa while maintaining (or even improving) the detection of csPCa, as compared to systematic biopsy. However, MRI findings must be interpreted in the light of the *a priori* risk of csPCa. Risk stratification combining clinical data, MRI findings and (maybe) other biomarkers will help, in the future, defining those patients that can safely avoid biopsy. Second, the inter-reader reproducibility of MRI is moderate at best. Current biopsy-targeting methods remain imprecise and their accuracy is substantially impacted by the operator's experience. As a result, 3 to 5 biopsy cores per target may be needed to reduce the risk of missing or undersampling the lesion, even with US/MR fusion systems. Other 'extended' MRI-targeted and perilesional biopsy templates are being investigated (see Section 5.2.7.1.4). Third, the use of pre-biopsy MRI may induce grade shift, even with the use of an aggregated ISUP grade for each MR lesion targeted at biopsy (see Section 5.2.4.2.6). Clinicians must interpret MRI-targeted biopsy results in the context of this potential grade shift. A revision of the definitions of the risk groups will be needed in the future to take into account wider use of MRI and MRI-targeted biopsy.

Finally, it must be emphasized that the 'MR pathway' has only been evaluated in patients in whom the risk of csPCa was judged high enough to deserve biopsy based on standard clinical assessment including PSA. Magnetic resonance imaging in individuals without any suspicion of PCa is likely to result in an increase in false-positive findings and subsequent unnesssary biopsies.

5.2.4.3 *Guidelines for MRI imaging in biopsy decision*

Introductory statement	LE
Systematic biopsy is an acceptable approach in case MRI is unavailable.	3

Recommendations for all patients	Strength rating
Do not use magnetic resonance imaging (MRI) as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for MRI acquisition and interpretation and evaluate MRI results in multidisciplinary meetings with pathological feedback.	Strong

Recommendations for biopsy-naïve patients	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.	Strong
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is low (e.g. PSA density < 0.15 ng/mL), omit biopsy based on shared decision-making with the patient.	Weak

Recommendations for patients with prior negative biopsy	Strength rating
Perform MRI before prostate biopsy.	Strong
When MRI is positive (i.e. PI-RADS ≥ 3), perform targeted biopsy only.	Weak
When MRI is negative (i.e., PI-RADS ≤ 2), and clinical suspicion of PCa is high, perform systematic biopsy based on shared decision-making with the patient.	Strong

5.2.5 ***Baseline biopsy decision***

The need for prostate biopsy is based on PSA level, other biomarkers and/or suspicious DRE and/or imaging (see Section 5.2.4). Age, potential co-morbidity and therapeutic consequences should also be considered and discussed beforehand [253]. Risk stratification is a potential tool for reducing unnecessary biopsies [285].

Limited PSA elevation alone should not prompt immediate biopsy. Prostate-specific antigen level should be verified after a few weeks, in the same laboratory using the same assay under standardised conditions (i.e. no ejaculation, manipulations, and urinary tract infections [UTIs]) [286, 287]. Empiric use of antibiotics in an asymptomatic patient in order to lower the PSA should not be undertaken [288].

Ultrasound (US)-guided and/or MRI-targeted biopsy is now the SOC. Prostate biopsy is performed by either the transrectal or transperineal approach. Cancer detection rates, when performed without prior imaging with MRI, are comparable between the two approaches [257], however, some evidence suggests reduced infection risk with the transperineal route (see Section 5.2.6.4) [289, 290]. Transurethral resection of the prostate (TURP) should not be used as a tool for cancer detection [291].

5.2.6 ***Repeat biopsy decision***

5.2.6.1 *Repeat biopsy after previously negative biopsy*

Men with a previous negative systematic biopsy should be offered a prostate MRI and in case of PIRADS > 3 findings, a repeat (targeted) biopsy has to be done. Other indications for repeat biopsy are:

- rising and/or persistently elevated PSA (see Table 5.3 for risk estimates);
- suspicious DRE, 5–30% PCa risk [179, 180];
- intraductal carcinoma as a solitary finding, > 90% risk of associated high-grade PCa [292];

In a contemporary series of biopsies the likelihood of finding a csPCa after follow-up biopsy after a diagnosis of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia (PIN) was only 6-8%, not significantly different from follow-up biopsies after a negative biopsy [293, 294].

The added value of other biomarkers remains unclear (see Sections 5.2.3.1 and 5.2.3.2).

5.2.6.2 *Saturation biopsy*

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30–43% and depends on the number of cores sampled during earlier biopsies [295]. Saturation biopsy may be performed with the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention varies substantially from 1.2% to 10% [296-299].

*5.2.7 **Prostate biopsy procedure***

5.2.7.1 Sampling sites and number of cores

5.2.7.1.1 Ultrasound-guided systematic biopsy

For systematic biopsies, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland regardless of the approach used. Sextant biopsy is no longer considered adequate. At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc [3]. Ten to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive [300, 301].

Additional cores should be obtained from suspect areas identified by DRE or on pre-biopsy MRI; multiple (3–5) cores should be taken from each MRI-visible lesion (see Section 5.2.4.2.7.2). They can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique over another [250, 302-305].

5.2.7.1.2 Ultrasound-guided saturation biopsy

In the setting of a positive MRI with targeted biopsy cores being taken, the addition of template cores may increase the detection of significant cancer slightly, but also increases the detection of insignificant cancer [103, 307]. The rationale for this must be careful considered on an individual patient basis.

5.2.7.1.3 MRI-directed targeted biopsy

Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique over another [250, 302-305]. However, regarding approach, the only systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%) [306]. This benefit was especially pronounced for anterior tumours. Multiple (3–5) cores should be taken from each lesion (see Section 5.2.4.2.7.2).

5.2.7.1.4 Towards ‘extended’ MRI-directed biopsy?

As detailed in Section 5.2.4.2.6.2, the added value of systematic biopsy is partially explained by the fact that they compensate for guiding imprecisions of targeted biopsy. Therefore, biopsy strategies with multiple peri-lesional (regional) targeted cores obtained in addition of MRI-directed targeted cores are being investigated [261, 262, 307-310]. Prospective clinical trials are needed to evaluate whether these strategies can replace the combination of systematic and targeted biopsy currently recommended as the diagnostic work-up in men with positive MRI scans.

*5.2.8 **Summary of evidence and guidelines for prostate biopsies***

Summary of evidence	**LE**
Literature review including multiple biopsy schemes suggests that a 10 to 12-core scheme is optimal in the majority of initial and repeat biopsy patients, dependent on prostate size. These biopsy schemes should be heavily weighted towards the lateral aspect and the apex of the prostate to maximize peripheral zone sampling [3].	3
A systematic review and meta-analysis comparing MRI-targeted transrectal biopsy to MRI-targeted transperineal biopsy, analysing 8 studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%).	2
Current literature, including systematic reviews and meta-analyses, does not show a clear superiority of one image-guided technique (cognitive guidance, US/MR fusion software or direct in-bore guidance) over the other.	2

Recommendations	**Strength rating***
At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc and 10 to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive.	Strong
Transperineal biopsies are preferred over transrectal biopsies.	Strong
Where MRI has shown a suspicious lesion MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance.	Weak

5.2.8.1 Antibiotics prior to biopsy

5.2.8.1.1 Transperineal prostate biopsy

A total of seven randomised studies including 1,330 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (37 events among 657 men) compared to transperineal biopsy (22 events among 673 men) (RR: 1.81 [range 1.09–3.00], 95% CI) [311-318]. In addition, a systematic review including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [319]. Finally, a population-based study from the UK, including 486,467 biopsies over more than a decade from 2008-2019, showed lower rates of sepsis and infection with transperineal vs. transrectal biopsy (0.53% vs. 0.31%, $p \leq 0.001$) [320]. The available evidence demonstrates that the transrectal approach should be abandoned in favour of the transperineal approach despite any possible logistical challenges.

To date, no RCT has been published investigating different antibiotic prophylaxis regimens for transperineal prostate biopsy. However, as it is a clean procedure that avoids rectal flora, quinolones or other antibiotics to cover rectal flora may not be necessary. A single dose of cephalosporin only to cover skin commensals has been shown to be sufficient in multiple single cohort series [299, 321]. Prior negative mid-stream urine test and routine surgical disinfecting preparation of the perineal skin are mandatory. In one of the largest studies to date, 1,287 patients underwent transperineal biopsy under local anaesthesia only [322]. Antibiotic prophylaxis consisted of a single oral dose of either cefuroxime or cephalexin. Patients with cardiac valve replacements received amoxycillin and gentamicin, and those with severe penicillin allergy received sulphamethoxazole. No quinolones were used. Only one patient developed a UTI with positive urine culture and there was no urosepsis requiring hospitalisation.

In another study of 577 consecutive patients undergoing transperineal biopsy using single dose IV cephazolin prophylaxis, one patient (0.2%) suffered prostatitis not requiring hospitalisation [299]. There were no incidences of sepsis. In a further study of 485 patients using only cephazolin, 4 patients (0.8%) suffered infectious complications [323].

5.2.8.1.2 Transrectal prostate biopsy

Meta-analysis of eight RCTs including 1,786 men showed that use of a rectal povidone-iodine preparation before biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications (RR: 0.55, 95% CI: 0.41–0.72) [318, 324-329]. Single RCTs showed no evidence of benefit for perineal skin disinfection [330], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [331].

A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications (RR: 0.96, 95% CI: 0.64–1.54) [318, 332-334].

A meta-analysis of 26 RCTs with 3,857 patients found no evidence that use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than no injection (RR: 1.07, 95% CI: 0.77–1.48) [318]. A meta-analysis of 9 RCTs including 2,230 patients found that extended biopsy templates showed comparable infectious complications to standard templates (RR: 0.80, 95% CI: 0.53–1.22) [318]. Additional meta-analyses found no difference in infections complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. non-coaxial), needle size (large vs. small), and number of injections for peri-prostatic nerve block (standard vs. extended) [318].

A meta-analysis of eleven studies including 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control (RR: 0.56, 95% CI:0.40–0.77) [335].

Fluoroquinolones have been traditionally used for antibiotic prophylaxis in this setting; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones resulting in the suspension of the indication for peri-operative antibiotic prophylaxis including prostate biopsy [336].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, or augmented prophylaxis (combination of two or more different classes of antibiotics) is recommended [335]. In countries where use of fluoroquinolones are suspended, cephalosporins or aminoglycosides can be used as individual agents with comparable infectious complications based on a meta-analysis of two RCTs [335]. A meta-analysis of three RCTs reported that fosfomycin trometamol was superior to fluoroquinolones (RR: 0.49, 95% CI: 0.27–0.87) [335], but routine general use should be critically

assessed due to the relevant infectious complications reported in non-randomised studies [337]. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swap/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See figure 5.1 for prostate biopsy workflow to reduce infections complications.

Based on a meta-analysis, suggested antimicrobial prophylaxis before transrectal biopsy may consist of:

1. Targeted prophylaxis - based on rectal swab or stool culture.
2. Augmented prophylaxis - two or more different classes of antibiotics (of note: this option is against antibiotic stewardship programmes).
3. Alternative antibiotics:
    - fosfomycin trometamol (e.g., 3 g before and 3 g 24–48 hrs. after biopsy);
    - cephalosporin (e.g., ceftriaxone 1 g i.m; cefixime 400 mg p.o for 3 days starting 24 hrs. before biopsy) aminoglycoside (e.g., gentamicin 3 mg/kg i.v.; amikacin 15 mg/kg i.m).

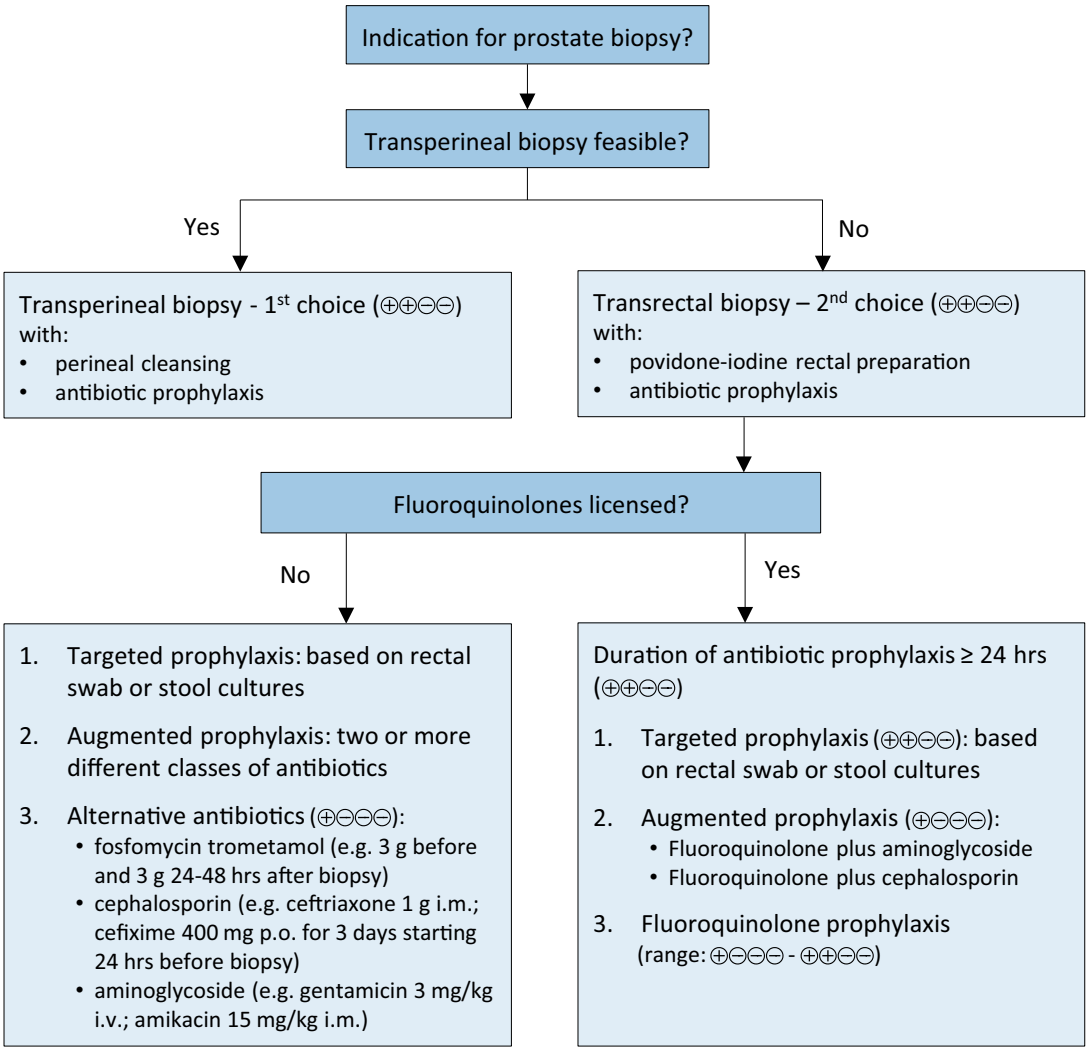
5.2.8.2 Summary of evidence and recommendations for performing prostate biopsy (in line with the EAU Urological Infections Guidelines Panel)

Summary of evidence	**LE**
A meta-analysis of seven studies including 1,330 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight RCTs including 1,786 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

Recommendations	**Strength rating***
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong
Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g., fosfomycin trometamol, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak
Use a single oral dose of either cefuroxime or cephalexin or cephazolin as antibiotic prophylaxis for transperineal biopsy. Patients with severe penicillin allergy may be given sulphamethoxazole.	Weak
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong

*Note on strength ratings:
The above strength ratings are explained here due to the major clinical implications of these new recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its Strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy as, although quality of data is low, the clinical benefit is high and practical application simple. A 'Strong' rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.

Figure 5.1: Prostate biopsy workflow to reduce infectious complications*


Indication for prostate biopsy?
Transperineal biopsy feasible?
Yes
No
Transperineal biopsy - 1st choice (⊕⊕⊖⊖) with:
• perineal cleansing
• antibiotic prophylaxis
Transrectal biopsy – 2nd choice (⊕⊕⊖⊖) with:
• povidone-iodine rectal preparation
• antibiotic prophylaxis
Fluoroquinolones licensed?
No
Yes
1. Targeted prophylaxis: based on rectal swab or stool cultures
2. Augmented prophylaxis: two or more different classes of antibiotics
3. Alternative antibiotics (⊕⊖⊖⊖):
• fosfomycin trometamol (e.g. 3 g before and 3 g 24-48 hrs after biopsy)
• cephalosporin (e.g. ceftriaxone 1 g i.m.; cefixime 400 mg p.o. for 3 days starting 24 hrs before biopsy)
• aminoglycoside (e.g. gentamicin 3 mg/kg i.v.; amikacin 15 mg/kg i.m.)
Duration of antibiotic prophylaxis ≥ 24 hrs (⊕⊕⊖⊖)
1. Targeted prophylaxis (⊕⊕⊖⊖): based on rectal swab or stool cultures
2. Augmented prophylaxis (⊕⊖⊖⊖):
• Fluoroquinolone plus aminoglycoside
• Fluoroquinolone plus cephalosporin
3. Fluoroquinolone prophylaxis (range: ⊕⊖⊖⊖ - ⊕⊕⊖⊖)

GRADE Working Group grades of evidence.

- *High certainty: (⊕⊕⊕⊕) very confident that the true effect lies close to that of the estimate of the effect.*
- *Moderate certainty: (⊕⊕⊕⊖) moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
- *Low certainty: (⊕⊕⊖⊖) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.*
- *Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.*

**Figure adapted from Pilatz et al., [338] with permission from Elsevier.*

5.2.8.3 Local anaesthesia prior to biopsy

Ultrasound-guided peri-prostatic block is recommended [339]. It is not important whether the depot is apical or basal. Intra-rectal instillation of local anaesthesia is inferior to peri-prostatic infiltration [340]. Local anaesthesia can also be used effectively for MRI-targeted and systemic transperineal biopsy [341]. Patients are placed in the lithotomy position. Bupivacaine is injected into the perineal skin and subcutaneous tissues, followed two minutes later by a peri-prostatic block. A systematic review evaluating pain in 3 studies comparing transperineal vs. transrectal biopsies found that the transperineal approach significantly increased patient pain (RR: 1.83 [1.27–2.65]) [342]. In a randomised comparison a combination of peri-prostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to peri-prostatic anaesthesia only [343]. Targeted biopsies can then be taken via a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [341, 344, 345].

5.2.8.4 Complications

Complications of TRUS biopsy are listed in Table 5.6 [316]. Mortality after prostate biopsy is extremely rare and most are consequences of sepsis [126]. Low-dose aspirin is no longer an absolute contraindication [346].

A systematic review found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haematospermia and urinary retention [347]. A meta-analysis of 4,280 men randomised between transperineal vs. TRUS biopsies in 13 studies found no significant differences in complication rates, however, data on sepsis compared only 497 men undergoing TRUS biopsy to 474 having transperineal biopsy. The transperineal approach required more (local) anaesthesia [348].

Table 5.6: Percentage of complications per TRUS biopsy session, irrespective of the number of cores

Complications	Percentage of patients affected
Haematospermia	37.4
Haematuria > 1 day	14.5
Rectal bleeding < 2 days	2.2
Prostatitis	1.0
Fever > 38.5°C	0.8
Epididymitis	0.7
Rectal bleeding > 2 days +/– surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

5.2.8.5 Seminal vesicle biopsy

Indications for SV (staging) biopsies are poorly defined. At a PSA of > 15 ng/mL, the odds of tumour involvement are 20–25% [349]. A SV staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent RT. Its added value compared with MRI is questionable.

5.2.8.6 Transition zone biopsy

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to MRI-detected lesions or repeat biopsies [350].

5.2.9 ***Pathology of prostate needle biopsies***

5.2.9.1 Processing

Prostate core biopsies from different sites are processed separately. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [351]. To achieve optimal flattening and alignment, a maximum of three cores should be embedded per tissue cassette, and sponges or paper used to keep the cores stretched and flat [352, 353]. To optimise detection of small lesions and improve accuracy of grading, paraffin blocks should be cut at three levels and intervening unstained sections may be kept for immunohistochemistry (IHC) [354].

5.2.9.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [354-356]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [354]. Section 5.2.8.3 lists the recommended terminology for reporting prostate biopsies [352]. Type and subtype of PCa should be reported such as for instance acinar adenocarcinoma (> 95% of PCa), ductal adenocarcinoma (< 5%) and poorly differentiated small or large cell neuroendocrine carcinoma (< 1%), even if representing a small proportion of the PCa. The distinct aggressive nature of ductal adenocarcinoma and small/large cell neuroendocrine carcinoma should be commented upon in the pathology report [352]. Considerable evidence has been accumulated in recent years supporting that among the Gleason grade 4 patterns, the expansile cribriform pattern carries an increased risk of biochemical recurrence, metastatic disease and death of disease [357, 358]. Reporting of this sub-pattern based on established criteria) is recommended [89, 359]. Intraductal carcinoma, defined as an extension of cancer cells into pre-existing prostatic ducts and acini, distending them, with preservation of basal cells [89], should be distinguished from high-grade PIN [360] as it conveys unfavourable prognosis in terms of biochemical recurrence and cancer-specific survival (CSS) [361, 362]. Its presence should be reported, whether occurring in isolation or associated with adenocarcinoma [89].

5.2.9.2.1 Recommended terminology for reporting prostate biopsies [287]

Recommendations	Strength rating
Benign/negative for malignancy; if appropriate, include a description.	Strong
Active inflammation.	
Granulomatous inflammation.	
High-grade prostatic intraepithelial neoplasia (PIN).	
High-grade PIN with atypical glands, suspicious for adenocarcinoma (PINATYP).	
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer.	
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern.	
Intraductal carcinoma.	

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the ISUP 2014 grade [88]. For MRI targeted biopsies consisting of multiple cores per target the aggregated (or composite) ISUP grade and percentage of high-grade carcinoma should be reported per targeted lesion [89]. If the targeted biopsies are negative, presence of specific benign pathology should be mentioned, such as dense inflammation, fibromuscular hyperplasia or granulomatous inflammation [89, 363]. A global ISUP grade comprising all systematic (non-targeted) and targeted biopsies is also reported (see Section 4.2). The global ISUP grade takes into account all biopsies positive for carcinoma, by estimating the total extent of each Gleason grade present. For instance, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site of Gleason grade 4 only, the global ISUP grade would be 2 (i.e. GS 7[3+4]) or 3 (i.e. GS 7[4+3]), dependent on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the worse grade would be ISUP grade 4 (i.e. GS 8[4+4]). Recent publications demonstrated that global ISUP grade is somewhat superior in predicting prostatectomy ISUP grade [364] and BCR [365].

Lymphovascular invasion (LVI) and EPE must each be reported, if identified, since both carry unfavourable prognostic information [366-368].

The proportion of systematic (non-targeted) carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP grade, tumour volume, surgical margins and pathologic stage in RP specimens and predict BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathologic stage and SV invasion after RP and RT failure [369-371]. A pathology report should therefore provide both the proportion of carcinoma-positive cores and the extent of cancer involvement for each core. The length in mm and percentage of carcinoma in the biopsy have equal prognostic impact [372]. An extent of > 50% of adenocarcinoma in a single core is used in some AS protocols as a cut off [373] triggering immediate treatment vs. AS in patients with ISUP grade 1 (see Section 6.1.1.2).

A prostate biopsy that does not contain glandular tissue should be reported as diagnostically inadequate.
Mandatory elements to be reported for a carcinoma-positive prostate biopsy are:

- type of carcinoma;
- primary and secondary/worst Gleason grade (per biopsy site and global);
- International Society of Urological Pathology grade (global);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (per biopsy site);
- if present: EPE, SV invasion, LVI, intraductal carcinoma/cribriform pattern, peri-neural invasion;
- For MRI-targeted biopsies with multiple cores report aggregate (or composite) ISUP grade and percentage high-grade carcinoma per targeted site;
- For carcinoma-negative MRI-targeted biopsy report specific benign pathology, e.g., fibromuscular hyperplasia or granulomatous inflammation, if present [89].

5.2.9.3 Tissue-based prognostic biomarker testing

After a comprehensive literature review and several panel discussions an ASCO-EAU-AUA multidisciplinary expert panel made recommendations regarding the use of tissue-based PCa biomarkers. The recommendations were limited to 5 commercially available tests (Oncotype Dx®, Prolaris®, Decipher®, Decipher PORTOS and ProMark®) with extensive validation in large retrospective studies and evidence that their test results might actually impact clinical decision-taking [374].

The selected commercially available tests significantly improved the prognostic accuracy of clinical multivariable models for identifying men who would benefit of AS and those with csPCa requiring curative treatment, as well as for guidance of patient management after RP. In addition, a few studies showed that tissue biomarker tests and MRI findings independently improved the detection of csPCa in an AS setting, but it remains unclear which men would benefit of both tests. Since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa scheduled for RT to decide on treatment intensification with hormonal therapy (HT).

5.2.9.4 Histopathology of radical prostatectomy specimens

5.2.9.4.1 Processing of radical prostatectomy specimens

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens are totally embedded to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding may also be considered, particularly for prostates > 60 g. The most widely accepted method includes complete embedding of the posterior prostate and a single mid-anterior left and right section. Compared with total embedding, partial embedding with this method missed 5% of positive margins and 7% of extraprostatic extension [375].

The entire RP specimen should be inked upon receipt in the laboratory to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. Fixation can be enhanced by injecting formalin which provides more homogeneous fixation and sectioning after 24 hours [376]. After fixation, the apex and the base (bladder neck) are removed and cut into (para)sagittal or radial sections; the shave method is not recommended [87]. The remainder of the specimen is cut in transverse, 3–4 mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole-mounts or after quadrant sectioning. Whole-mounts provide better topographic visualisation, faster histopathological examination and better correlation with pre-operative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.2.9.4.1.1 Guidelines for processing prostatectomy specimens

Recommendations	Strength rating
Ensure total embedding, by conventional (quadrant) or whole-mount sectioning.	Strong
Ink the entire surface before cutting, to evaluate the surgical margin.	Strong
Examine the apex and base separately, using the cone method with sagittal or radial sectioning.	Strong

5.2.9.4.2 Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.7). As a result of the complex information to be provided for each RP specimen, the use of synoptic(-like) or checklist reporting is recommended (Table 5.8). Synoptic reporting results in more transparent and complete pathology reporting [377].

Table 5.7: Mandatory elements provided by the pathology report

Histopathological type: > 95% of PCa represents conventional (acinar) adenocarcinoma.
Grading according to ISUP grade (or not applicable if therapy-related changes).
Presence of intraductal and/or cribriform carcinoma.
Tumour (sub)staging and surgical margin status: location and extent of EPE, presence of bladder neck invasion, laterality of EPE or SV invasion, location and extent of positive surgical margins.
Additional information may be provided on multifocality, and diameter/volume and zonal location of the dominant tumour.

Table 5.8: Example checklist: reporting of prostatectomy specimens

Histopathological (sub)type
Type of carcinoma, e.g. conventional acinaradenocarcinoma, (small cell) neuroendocrine cell carcinoma or ductal
Subtype, e.g. conventional acinar, ductal, mucinous
Histological grade
Primary (predominant) Gleason grade Secondary Gleason grade Tertiary Gleason grade (if applicable) Global ISUP grade Approximate percentage of Gleason grade 4 or 5
Tumour quantitation (optional)
Percentage of prostate involved Size/volume of dominant tumour nodule
Pathological staging (pTNM)
If extraprostatic extension is present: • indicate whether it is focal or extensive (see Section 5.2.9.4.4); • specify sites; • indicate whether there is seminal vesicle invasion. *If applicable, regional lymph nodes:* • location; • number of nodes retrieved; • number of nodes involved.
Surgical margins
If carcinoma is present at the margin: • specify sites; • Extent: focal or extensive (see Section 5.2.9.4.6) • (highest) grade at margin.
Other
Presence of lymphovascular/angio-invasion Location of dominant tumour Presence of intraductal carcinoma/cribriform architecture

5.2.9.4.3 ISUP grade in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the (ISUP 2014 modified) Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [88]. The ISUP grade is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [378].

The ISUP grade is based on the sum of the most and second-most dominant (in terms of volume) Gleason grade. ISUP grade 1 is GS 6. ISUP grades 2 and 3 represent carcinomas constituted of Gleason grade 3 and 4 components, with ISUP grade 2 when 50% of the carcinoma, or more, is Gleason grade 3 and ISUP grade 3 when the grade 4 component represents more than 50% of the carcinoma. In a carcinoma almost entirely composed of Gleason grade 3 the presence of a minor (< 5%) Gleason pattern 4 component is not included in the GS (ISUP grade 1), but its presence is commented upon.

ISUP grade 4 is largely composed of Gleason grade 4 and ISUP grade 5 of a combination of Gleason grade 4 and 5 or only Gleason grade 5. A global ISUP grade is given for multiple tumours, but a separate tumour focus with a higher ISUP grade should also be mentioned. Tertiary Gleason grade 5, if > 5% of the PCa volume, is an unfavourable prognostic indicator for BCR and should be incorporated in the ISUP grade. If less than 5% its presence should be mentioned in the report as minor grade component [89, 379].

5.2.9.4.4 Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with peri-prostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g., neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE because the latter is related to recurrence risk [380].

There are no internationally accepted definitions of focal or microscopic, vs. non-focal or extensive EPE. Some describe focal as a few glands [381] or < 1 high-power field in one or at most two sections [382] whereas others measure the depth of extent in millimetres [383].

At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e. not as pT4, because it does not carry independent prognostic significance for PCa recurrence and should be recorded as EPE (pT3a) [384, 385]. Stage pT4 is only assigned when the tumour invades the bladder muscle wall as determined macroscopically [386].

5.2.9.4.5 PCa volume

The independent prognostic value of PCa volume in RP specimens has not been established [382, 387-390]. Nevertheless, a cut-off of 0.5 mL is traditionally used to distinguish insignificant from clinically relevant cancer [387]. Improvement in prostatic radio-imaging allows more accurate pre-operative measurement of cancer volume. It is recommended that at least the diameter/volume of the dominant tumour nodule should be assessed, or a rough estimate of the percentage of cancer tissue provided [391].

5.2.9.4.6 Surgical margin status

Surgical margin is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [388] or at the surface of the tissue lacking ink. In tissues that have severe crush artefacts, it may not be possible to determine margin status [392].

Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [393]. There is evidence for a relationship between margin extent and recurrence risk [394, 395]. However, some indication must be given of the multifocality and extent of margin positivity, such as the linear extent in mm of involvement: focal, ≤ 1 mm vs. extensive, > 1 mm [396], or number of blocks with positive margin involvement. Gleason score at the positive margin was found to correlate independently with outcome, and should be reported [394, 397].

5.3 Diagnosis - Clinical Staging

*5.3.1 **T-staging***

The cT category used in the risk table only refers to the DRE finding. The imaging parameters and biopsy results for local staging are, so far, not part of the risk category stratification [398].

5.3.1.1 TRUS

Transrectal US is no more accurate at predicting organ-confined disease than DRE [399]. Some single-centre studies reported good results in local staging using 3D TRUS or colour Doppler but these good results were not confirmed by large-scale studies [400, 401].

5.3.1.2 MRI

T2-weighted imaging remains the most useful method for local staging on MRI. Pooled data from a meta-analysis showed a sensitivity and specificity of 0.57 (95% CI: 0.49–0.64) and 0.91 (95% CI: 0.88–0.93), 0.58 (95% CI: 0.47–0.68) and 0.96 (95% CI: 0.95–0.97), and 0.61 (95% CI: 0.54–0.67) and 0.88 (95% CI: 0.85–0.91), for EPE, SVI, and overall stage T3 assessment, respectively [402].

Detection of EPE and SVI seems more accurate at high field strength (3 Tesla) [402], while the added value of functional imaging remains debated [402, 403].

In 552 men treated by RP at seven different Dutch centres, MRI showed significantly higher sensitivity (51% vs. 12%; $p < 0.001$), and lower specificity (82% vs. 97%; $p < 0.001$) than DRE for non-organ confined disease. All risk groups redefined using MRI findings rather than DRE findings showed better BCR-free survival due to improved discrimination and the Will Roger's phenomenon [404].

Traditionally, EPE/SVI is diagnosed on MRI using direct qualitative signs (e.g., irregular bulging of the prostate, capsular disruption, visible tumour within periprostatic fat, obliteration of the rectoprostatic angle, asymmetry of the neurovascular bundles or focal low signal intensity in the SVs) [405]. With such subjective reading, experience of the reader remains of paramount importance [406] and the inter-reader agreement is moderate with kappa (κ) values ranging from 0.41 to 0.68 [407]. The length of tumour capsule contact (LCC) is also a significant predictor of EPE; it has the advantage of being quantitative, although the ideal cut-off value remains debated [408]. Several grading systems combining subjective qualitative signs and/or LCC into a score have shown good sensitivity for EPE (0.68–0.82) with substantial inter-reader agreement (κ = 0.63–0.74), but at the expense of decreased specificity (0.71–0.77); none of these scores has shown definitive superiority over the others [409].

Magnetic resonance imaging findings can improve the prediction of the pathological stage when combined with clinical and biopsy data. As a result, several groups developed multivariate risk calculators for predicting

EPE/SVI or positive surgical margins [410]. In external validation cohorts, these risk calculators showed significantly better discrimination than nomograms without MRI-based features [411-413]. However, they remain limited by substantial miscalibration and therefore their results must be interpreted with care.

Given its low sensitivity for focal (microscopic) EPE, MRI is not recommended for local staging in low-risk patients [414-416]. However, MRI can still be useful for treatment planning.

*5.3.2 **N-staging***

5.3.2.1 Computed tomography and magnetic resonance imaging

Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of non-metastatic LNs varies widely and may overlap the size of LN metastases. Usually, LNs with a short axis > 8 mm in the pelvis and > 10 mm outside the pelvis are considered malignant. Decreasing these thresholds improves sensitivity but decreases specificity. As a result, the ideal size threshold remains unclear [417, 418]. Computed tomography and MRI sensitivity is less than 40% [419, 420]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade < 4 cancer, PSA < 20 ng/mL, or localised disease [421-423].

Diffusion-weighted MRI (DW-MRI) may detect metastases in normal-sized nodes, but a negative DW-MRI cannot rule out the presence of LN metastases, and DW-MRI provides only modest improvement for LN staging over conventional imaging [424].

5.3.2.2 Risk calculators incorporating MRI findings and clinical data

Because CT and MRI lack sensitivity for direct detection of positive LNs, nomograms combining clinical and biopsy findings have been used to estimate the risk of patients harbouring positive LNs [425-427]. Although these nomograms are associated with good performance, they have been developed using systematic biopsy findings and may therefore not be appropriate for patients diagnosed with combined MRI-targeted biopsy and systematic biopsy.

Two models incorporating MRI-targeted biopsy findings and MRI-derived findings recently underwent external validation [428, 429]. One model was tested on an external cohort of 187 patients with a prevalence of LN invasion of 13.9% (vs. 16.9% in the development cohort). The C-index was 0.73 (vs. 0.81 in the development cohort); at calibration analysis, the model tended to overpredict the actual risk [428]. The other model was validated in an external multi-centre cohort of 487 patients with a prevalence of 8% of LN invasion (vs. 12.5% in the development cohort). The AUC was 0.79 (vs. 0.81 in the development cohort). Using a risk cut-off of 7% would have avoided LN dissection in 273 (56% of the cohort), while missing LN invasion in 7 patients (2.6% of the patients below the 7% threshold; 18% of the 38 patients with LN invasion) [430]. Therefore, this nomogram and a 7% threshold should be used after MRI-targeted biopsy to identify candidates for extended lymph node dissection (eLND).

5.3.2.3 Choline PET/CT

In a meta-analysis of 609 patients, pooled sensitivity and specificity of choline PET/CT for pelvic LN metastases were 62% (95% CI: 51–66%) and 92% (95% CI: 89–94%), respectively [431]. In a prospective trial of 75 patients at intermediate risk of nodal involvement (10–35%), the sensitivity was only 8.2% at region-based analysis and 18.9% at patient-based analysis, which is too low to be of clinical value [432]. The sensitivity of choline PET/CT increases to 50% in patients at high risk and to 71% in patients at very high risk, in both cases out-performing contrast-enhanced CT [433]. Comparisons between choline PET/CT and DW-MRI yielded contradictory results [432, 434-436].

Due of its low sensitivity, choline PET/CT does not reach clinically acceptable diagnostic accuracy for detection of LN metastases, or to rule out a nodal dissection based on risk factors or nomograms (see Section 6.3.4.1.2).

5.3.2.4 Prostate-specific membrane antigen-based PET/CT

Prostate-specific membrane antigen (PSMA) positron-emission tomography (PET)/CT uses several different radiopharmaceuticals; most published studies used ^{68}Ga-labelling for PSMA PET imaging, but some used ^{18}F-labelling. At present there are no conclusive data about comparison of such tracers, with additional new radiotracers being developed. Prostate-specific membrane antigen is also an attractive target because of its specificity for prostate tissue, even if the expression in other non-prostatic malignancies or benign conditions may cause incidental false-positive findings [437-441].

A prospective, multi-centre study addressed the use of ^{68}Ga-PSMA PET/CT in patients with newly diagnosed PCa and negative bone scan findings. Positron-emission tomography was positive in 17 patients, resulting in a per-patient-based sensitivity and specificity of 41.5% (95% CI: 26.7–57.8) and 90.9% (95% CI: 79.3–96.6), respectively. A treatment change occurred in 12.6% of patients [442]. Another prospective multi-centre trial

investigated the diagnostic accuracy of ^{18}F-DCFPyL PET/CT for LN staging in 117 patients with primary PCa, prior to RP with ePLND. ^{18}F-DCFPyL PET/CT showed a high specificity (94.0%; CI: 86.9–97.5%), and a limited sensitivity (41.2%,CI: 19.4–66.5%) for the detection of pelvic LN metastases [443]. Comparable results were demonstrated in a phase II/III prospective, multi-centre study (OSPREY). In 252 evaluable patients with high risk of PCa who underwent RP with PLND, ^{18}F-DCFPyL PET/CT showed a median specificity of 97.9% (95% CI: 94.5–99.4%) and median sensitivity of 40.3% (28.1–52.5%) for pelvic nodal involvement [444]. This suggests that current PSMA-based PET/CT imaging cannot yet replace diagnostic ePLND.

Prostate-specific antigen may be a predictor of a positive PSMA PET/CT. In the primary staging cohort from a meta-analysis, however, no robust estimates of positivity were found [445]. The tracer uptake is also influenced by the ISUP grade. Similarly, patients with PSA levels ≥ 10 ng/mL showed significantly higher uptake than those with PSA levels < 10 ng/mL [446].

Comparison between PSMA PET/CT and MRI was performed in a systematic review and meta-analysis including 13 studies (n = 1,597) [447]. ^{68}Ga-PSMA was found to have a higher sensitivity and a comparable specificity for staging pre-operative LN metastases in intermediate- and high-risk PCa. Another prospective trial reported superior sensitivity of PSMA PET/CT as compared to MRI for nodal staging of 36 high-risk PCa patients [448].

PSMA PET/CT has a good sensitivity and specificity for LN involvement, possibly impacting clinical decision-making. In a review and meta-analysis including 37 articles, a subgroup analysis was performed in patients undergoing PSMA PET/CT for primary staging. On a per-patient-based analysis, the sensitivity and specificity of ^{68}Ga-PSMA PET were 77% and 97%, respectively, after eLND at the time of RP. On a per-lesion-based analysis, sensitivity and specificity were 75% and 99%, respectively [445].

In summary, PSMA PET/CT is more appropriate in N-staging as compared to MRI, abdominal contrast-enhanced CT or choline PET/CT; however, small LN metastases, under the spatial resolution of PET (~5 mm), may still be missed.

5.3.2.5 Risk calculators incorporating MRI and PSMA findings

Recently, an international, multi-centre study incorporated PSMA PET into existing nomograms in order to predict pelvic LN metastatic disease in PCa patients. Performance of 3 nomograms was assessed in 757 patients undergoing RARP and ePLND. Addition of PSMA PET to the nomograms substantially improved the discriminative ability of the models yielding cross-validated AUCs of 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively [449].

*5.3.3 **M-staging***

5.3.3.1 Bone scan

^{99m}Tc-Bone scan is a highly sensitive conventional imaging technique, evaluating the distribution of active bone formation in the skeleton related to malignant and benign disease. A meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%) at patient level [450]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade [417, 451]. A retrospective study investigated the association between age, PSA and GS in 703 newly diagnosed PCa patients who were referred for bone scintigraphy. The incidence of bone metastases increased substantially with rising PSA and upgrading GS [452]. In two studies, a dominant Gleason pattern of 4 was found to be a significant predictor of positive bone scan [453, 454]. Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP grade or clinical stage [417].

5.3.3.2 Fluoride PET and PET/CT, choline PET/CT and MRI

^{18}F-sodium fluoride (^{18}F-NaF) PET or PET/CT, similarly to bone scintigraphy, only assesses the presence of bone metastases. ^{18}F-NaF PET or PET/CT was reported to have similar specificity and superior sensitivity to bone scintigraphy for detecting bone metastases in patients with newly diagnosed high-risk PCa [455, 456]. However, in a prospective study ^{18}F-NaF PET showed no added value over bone scintigraphy in patients with newly diagnosed intermediate- or high-risk PCa and negative bone scintigraphy results [457]. Recently, the interobserver agreement for the detection of bone metastases and the accuracy of ^{18}F-NaF PET/CT in the diagnosis of bone metastases were investigated. Bone metastases were identified in 211 out of 219 patients with an excellent interobserver agreement, demonstrating that ^{18}F-NaF PET/CT is a robust tool for the detection of osteoblastic lesions in patients with PCa [458].

It remains unclear whether choline PET/CT is more sensitive than bone scan but it has higher specificity with fewer indeterminate bone lesions [446, 459, 460]. Choline PET/CT has also the advantage of detecting visceral and nodal metastases.

Diffusion-weighted whole-body and axial skeleton MRI are more sensitive than bone scan and targeted conventional radiography in detecting bone metastases in high-risk PCa. Whole-body MRI can also

detect visceral and nodal metastases; it was shown to be more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [461].

A meta-analysis found that whole-body MRI is more sensitive than choline PET/CT and bone scan for detecting bone metastases on a per-patient basis, although choline PET/CT had the highest specificity [450].

5.3.3.3 Prostate-specific membrane antigen-based PET/CT

A systematic review including 12 studies (n = 322) reported high variation in ^{68}Ga-PSMA PET/CT sensitivity for initial staging (range 33–99%; median sensitivity on per-lesion analysis 33–92%, and on per-patient analysis 66–91%), with good specificity (per-lesion 82–100%, and per-patient 67–99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [462]. Table 5.9 reports the data of the 5 studies including histopathologic correlation.

Table 5.9: PSMA PET/CT results in primary staging alone [462]

Study	Sensitivity (per lesion)	Specificity (per lesion)	PPV (per lesion)	NPV (per lesion)
Budaus	33%	100%	100%	69%
Herlemann	84%	82%	84%	82%
Van Leeuwen	58%	100%	94%	98%
Maurer	74%	99%	95%	94%
Rahbar	92%	92%	96%	85%

NPV = negative predictive value; PPV = positive predictive value.

One prospective multi-centre study evaluated changes in planned management before and after PSMA PET/CT in 108 intermediate- and high-risk patients referred for primary staging. As compared to conventional staging, additional LNs and bone/visceral metastases were detected in 25% and 6% of patients, respectively [463]; management changes occurred in 21% of patients. A retrospective review investigated the risk of metastases identified by ^{68}Ga-PSMA at initial staging in 1,253 patients (high-risk disease in 49.7%) [464]. Metastatic disease was identified by PSMA PET/CT in 12.1% of men, including 8.2% with a PSA level of < 10 ng/mL and 43% with a PSA level of > 20 ng/mL. Lymph node metastases were suspected in 107 men, with 47.7% outside the boundaries of an ePLND. Bone metastases were identified in 4.7%. In men with intermediate-risk PCa metastases were identified in 5.2%, compared to 19.9% with high-risk disease.

In the PSMA PET/CT prospective multi-centre study in patients with high-risk PCa before curative-intent surgery or RT (proPSMA), 302 patients were randomly assigned to conventional imaging with CT and bone scintigraphy or ^{68}Ga-PSMA-11 PET/CT. The primary outcome focused on the accuracy of first-line imaging for the identification of pelvic LN or distant metastases, using a predefined reference standard consisting of histopathology, imaging, and biochemistry at 6-month follow-up. Accuracy of ^{68}Ga-PSMA PET/CT was 27% (95% CI: 23–31) higher than that of CT and bone scintigraphy (92% [88–95] vs. 65% [60–69]; p < 0.0001). Conventional imaging had a lower sensitivity (38% [24–52] vs. 85% [74–96]) and specificity (91% [85–97] vs. 98% [95–100]) than PSMA PET/CT. Furthermore, ^{68}Ga-PSMA PET/CT scan prompted management change more frequently as compared to conventional imaging (41 [28%] men [21–36] vs. 23 [15%] men [10–22], p = 0.08), with less equivocal findings (7% [4–13] vs. 23% [17–31]) and lower radiation exposure (8.4 mSv vs. 19.2 mSv; p < 0.001) [465]. In a small study ^{18}F-PSMA-1007 PET/CT proved superior to whole-body MRI with DWI and Single-photon Emission Computed Tomography (SPECT) CT [466].

5.3.4 Summary of evidence and practical considerations on initial N/M staging

The field of non-invasive N- and M-staging of PCa patients is evolving very rapidly. Evidence shows that choline PET/CT, PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN- and bone metastases than the classical work-up with bone scan and abdominopelvic CT. In view of the evidence offered by the randomised, multi-centre proPSMA trial [465], replacing bone scan and abdominopelvic CT by more sensitive imaging modalities may be a consideration in patients with high-risk PCa undergoing initial staging. However, in absence of prospective studies demonstrating survival benefit, caution must be used when taking therapeutic decisions [467]. The prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown. In particular, it is unclear whether patients with metastases detectable only with PET/CT or whole-body MRI should be managed using systemic therapies, or whether they should be subjected to aggressive local and metastases-directed therapies [468].

Results from RCTs evaluating the management and outcome of patients with (and without) metastases detected by choline PET/CT, PSMA PET/CT and MRI are awaited before a decision can be made to treat patients based on the results of these tests [469].

5.3.5 *Summary of evidence and guidelines for staging of prostate cancer*

Summary of evidence	LE
PSMA PET/CT is more accurate for staging than CT and bone scan for high-risk disease but to date no outcome data exist to inform subsequent management.	1b

Recommendations	Strength rating
Any risk group staging	
Use pre-biopsy MRI for local staging information.	Weak
Low-risk localised disease	
Do not use additional imaging for staging purposes.	Strong
Intermediate-risk disease	
In ISUP grade 3, include at least cross-sectional abdominopelvic imaging and a bone-scan for metastatic screening.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong
When using PSMA PET or whole body MRI to increase sensitivity, be aware of the lack of outcome data of subsequent treatment changes.	Strong

5.4 Estimating life expectancy and health status

5.4.1 ***Introduction***

Evaluation of life expectancy and health status is important in clinical decision-making for screening, diagnosis, and treatment of PCa. Prostate cancer is common in older men (median age 68) and diagnoses in men > 65 will result in a 70% increase in annual diagnosis by 2030 in Europe and the USA [470, 471].

Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over 10 years life expectancy is considered mandatory for any benefit from local treatment and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCa-specific mortality (PCSM) and life expectancy of surgery vs. AS [472]. Although in a RCT the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR: 0.45), RP was associated with a reduced risk of metastases and use of androgen deprivation therapy (ADT) among older men (RR: 0.68 and 0.60, respectively) [473]. External beam RT shows similar cancer control regardless of age, assuming a dose of > 72 Gy when using intensity-modulated or image-guided RT [474].

Older men have a higher incidence of PCa and may be under-treated despite the high overall mortality rates [475, 476]. Of all PCa-related deaths 71% occur in men aged > 75 years [477], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [478-480]. In the USA, only 41% of patients aged > 75 years with intermediate- and high-risk disease received curative treatment compared to 88% aged 65–74 [481].

5.4.2 ***Life expectancy***

Life expectancy tables for European men are available online: https://ec.europa.eu/eurostat/web/productsdatasets/-/tps00205. Survival may be variable and therefore estimates of survival must be individualised. Gait speed is a good single predictive method of life expectancy (from a standing start, at usual pace, generally over 6 meters). For men at age 75, 10-year survival ranged from 19% < 0.4 m/s to 87%, for ≥ 1.4 m/s [482].

Figure 5.2: Predicted Median Life Expectancy by Age and Gait Speed for males* [482]

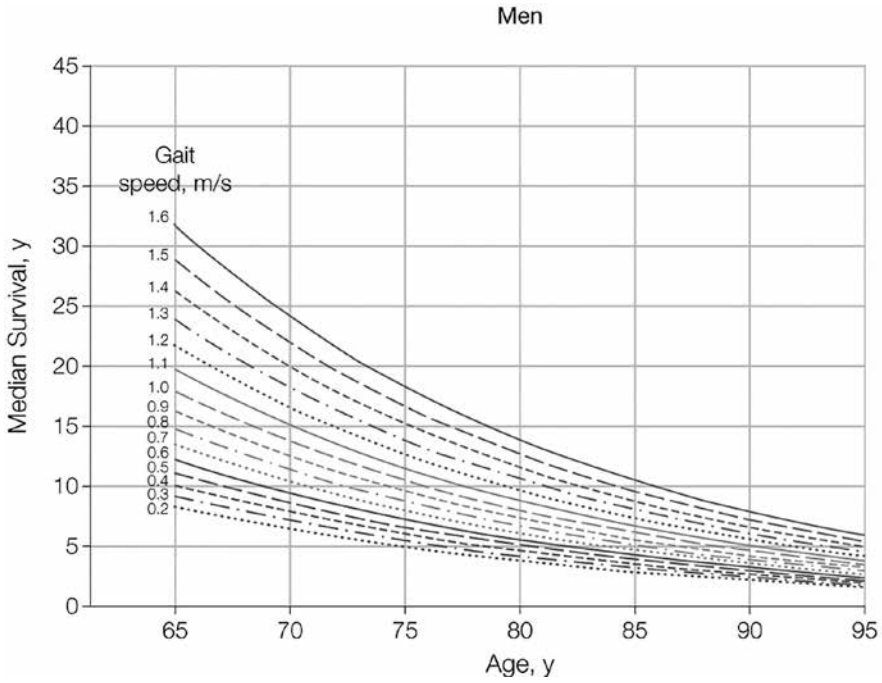


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5.4.3 ***Health status screening***

Heterogeneity increases with advancing age, so it is important to use measures other than just age or performance status (PS) when considering treatment options. The International SIOG PCa Working Group recommends that treatment for adults over 70 years of age should be based on a systematic evaluation of health status using the G8 (Geriatric 8) screening tool (see Table 5.10) [151]. This tool helps to discriminate between those who are fit and those with frailty, a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and negative side effects of cancer treatment [483]. Healthy patients with a G8 score > 14 or vulnerable patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Frail patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (see Figure 5.3) [151]. Patients with a G8 score ≤ 14 should undergo a comprehensive geriatric assessment (CGA) as this score is associated with 3-year mortality. A CGA is a multi-domain assessment that includes co-morbidity, nutritional status, cognitive and physical function, and social supports to determine if impairments are reversible [484]. A systematic review of the effect of geriatric evaluation for older cancer patients showed improved treatment tolerance and completion [485].

The Clinical Frailty Scale (CFS) is another screening tool for frailty (see Figure 5.4) [486]. Although not frequently used in the cancer setting, it is considered to be a common language for expressing degree of frailty. The scale runs from 1 to 9, with higher scores indicating increasing frailty. Patients with a higher CFS score have a higher 30-day mortality after surgery and are less likely to be discharged home [487].

It is important to use a validated tool to identify frailty, such as the G8 or CFS, as clinical judgement has been shown to be poorly predictive of frailty in older patients with cancer [488].

5.4.3.1 *Co-morbidity*

Co-morbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [489, 490]. Ten years after not receiving active treatment for PCa, most men with a high co-morbidity score had died from competing causes, irrespective of age or tumour aggressiveness [489]. Measures for co-morbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [491, 492] (Table 5.11) and Charlson Co-morbidity Index (CCI) [493].

5.4.3.2 *Nutritional status*

Malnutrition can be estimated from body weight during the previous 3 months (good nutritional status < 5% weight loss; risk of malnutrition: 5–10% weight loss; severe malnutrition: > 10% weight loss) [494].

5.4.3.3 Cognitive function

Cognitive impairment can be screened for using the mini-COG (https://mini-cog.com/) which consists of three-word recall and a clock-drawing test and can be completed within 5 minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an increasingly important factor in health status assessment [495-497]. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [498].

5.4.3.4 Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [499]. Measures for dependence in daily activities include: Activities of Daily Living (ADL; basic activities) and Instrumental Activities of Daily Living (IADL; activities requiring higher cognition and judgement) [500-502].

5.4.3.5 Shared decision-making

The patient's own values and preferences should be taken into account as well as the above factors. A shared decision-making process also involves anticipated changes to QoL, functional ability, and a patient's hopes, worries and expectations about the future [503]. Particularly in older and frail patients, these aspects should be given equal importance to disease characteristics during the decision-making process [504]. Older patients may also wish to involve family members, and this is particularly important where cognitive impairment exists.

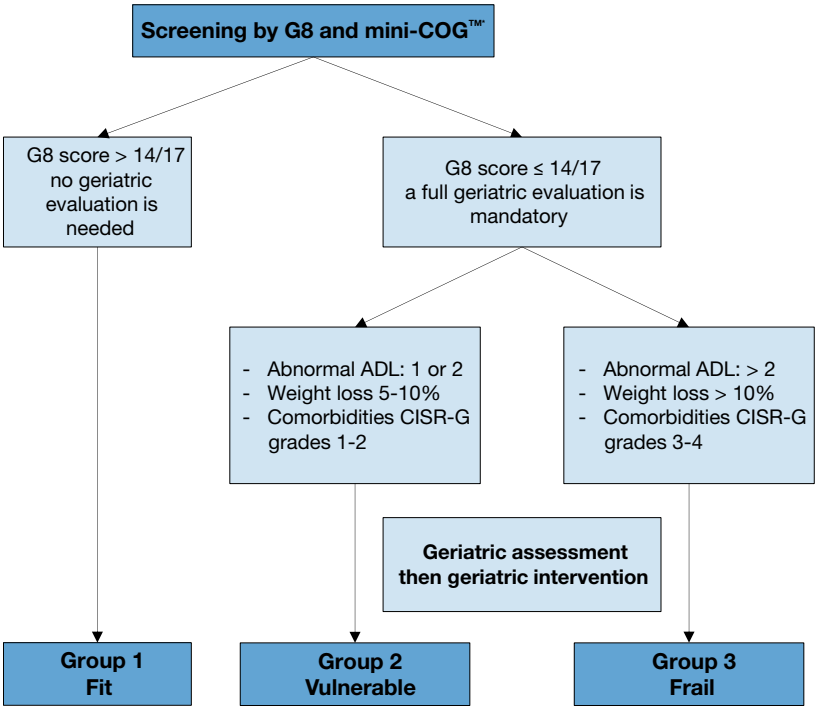
*5.4.4 **Conclusion***

Individual life expectancy, health status, frailty, and co-morbidity, not only age, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of 10 years is most commonly used as a threshold for benefit of local treatment. Older men may be undertreated. Patients aged 70 years of age or older who have frailty should receive a comprehensive geriatric assessment. Resolution of impairments in vulnerable men allows a similar urological approach as in fit patients.

Table 5.10: G8 screening tool (adapted from [505]**)**

	Items	**Possible responses (score)**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80-85
		2 = < 80
	Total score	**0-7**

Figure 5.3: Decision tree for health status screening (men > 70 years)** [151]

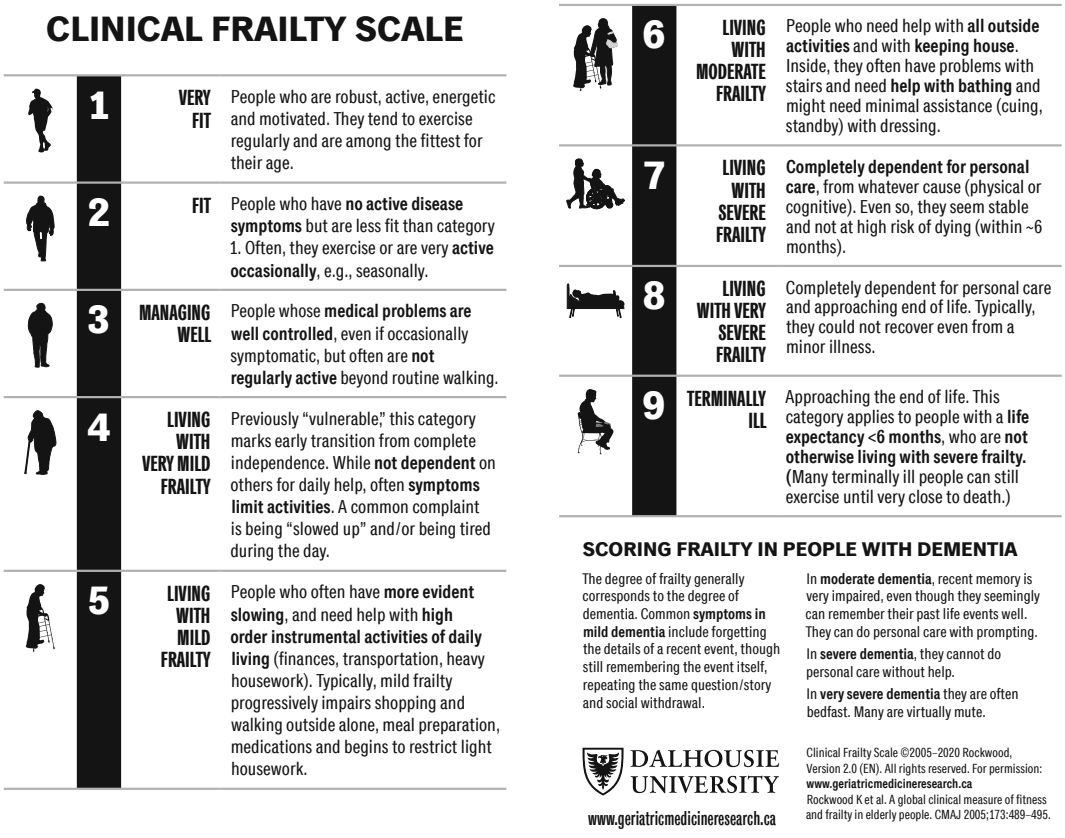

Screening by G8 and mini-COG™*
G8 score > 14/17
no geriatric evaluation is needed
G8 score ≤ 14/17
a full geriatric evaluation is mandatory
- Abnormal ADL: 1 or 2
- Weight loss 5-10%
- Comorbidities CISR-G grades 1-2
- Abnormal ADL: > 2
- Weight loss > 10%
- Comorbidities CISR-G grades 3-4
Geriatric assessment then geriatric intervention
Group 1 Fit
Group 2 Vulnerable
Group 3 Frail

Mini-COG™ = Mini-COG™ cognitive test; ADLs = activities of daily living; CIRS-G = Cumulative Illness Rating Score - Geriatrics; CGA = comprehensive geriatric assessment.

** For Mini-COG™, a cut-off point of ≤ 3/5 indicates a need to refer the patient for full evaluation of potential dementia.*

***Reproduced with permission of Elsevier, from Boyle H.J., et al. Eur J Cancer 2019:116; 116 [151].*

Figure 5.4: The Clinical Frailty Scale version 2.0 [486]*


CLINICAL FRAILTY SCALE
1 VERY FIT
People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
2 FIT
People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.
3 MANAGING WELL
People whose medical problems are well controlled, even if occasionally symptomatic, but often are not regularly active beyond routine walking.
4 LIVING WITH VERY MILD FRAILTY
Previously "vulnerable," this category marks early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up" and/or being tired during the day.
5 LIVING WITH MILD FRAILTY
People who often have more evident slowing, and need help with high order instrumental activities of daily living (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
6 LIVING WITH MODERATE FRAILTY
People who need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
7 LIVING WITH SEVERE FRAILTY
Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
8 LIVING WITH VERY SEVERE FRAILTY
Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
9 TERMINALLY ILL
Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death.)
SCORING FRAILTY IN PEOPLE WITH DEMENTIA
The degree of frailty generally corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.
In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
In severe dementia, they cannot do personal care without help.
In very severe dementia they are often bedfast. Many are virtually mute.
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Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

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Table 5.11: Cumulative Illness Score Rating-Geriatrics (CISR-G)

1	Cardiac (heart only)
2	Hypertension (rating is based on severity; affected systems are rated separately)
3	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics)
4	Respiratory (lungs, bronchi, trachea below the larynx)
5	ENT (eye, ear, nose, throat, larynx)
6	Upper GI (esophagus, stomach, duodenum. Biliar and parcreatic trees; do not include diabetes)
7	Lower GI (intestines, hernias)
8	Hepatic (liver only)
9	Renal (kidneys only)
10	Other GU (ureters, bladder, urethra, prostate, genitals)
11	Musculo-Skeletal-Integumentary (muscles, bone, skin)
12	Neurological (brain, spinal cord, nerves; do not include dementia)
13	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)
14	Psychiatric/Behavioural (includes dementia, depression, anxiety, agitation, psychosis)
	All body systems are scores on a 0 - 4 scale. - 0: No problem affecting that system. - 1: Current mild problem or past significant problem. - 2: Moderate disability or morbidity and/or requires first line therapy. - 3: Severe problem and/or constant and significant disability and/or hard to control chronic problems. - 4: Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.
Total score 0-56	

5.4.5 Guidelines for evaluating health status and life expectancy

Recommendations	Strength rating
Use individual life expectancy, health status, and co-morbidity in PCa management.	Strong
Use the Geriatric-8, Clinical Frailty Scale or mini-COG tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak
Offer adapted treatment to patients with irreversible impairment.	Weak
Offer symptom-directed therapy alone to frail patients.	Strong

6. TREATMENT

This chapter reviews the available treatment modalities, followed by separate sections addressing treatment for the various disease stages.

6.1 Treatment modalities

6.1.1 Deferred treatment (active surveillance/watchful waiting)

In localised disease a life expectancy of at least 10 years is considered mandatory for any benefit from active treatment. Data are available on patients who did not undergo local treatment with up to 25 years of follow-up, with endpoints of OS and CSS. Several series have shown a consistent CSS rate of 82–87% at 10 years [506-511], and 80–95% for T1/T2 and ISUP grade ≤ 2 PCas [512]. In three studies with data beyond 15 years, the DSS was 80%, 79% and 58% [508, 510, 511], and two reported 20-year CSS rates of 57% and 32%, respectively [508, 510]. The observed heterogeneity in outcomes is due to differences in inclusion criteria, with some older studies from the pre-PSA era showing worse outcomes [510]. In addition, many patients classified as ISUP grade 1 would now be classified as ISUP grade 2–3 based on the 2005 Gleason classification, suggesting that the above-mentioned results should be considered as minimal. Patients with well-, moderately- and poorly differentiated tumours had 10-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from the pooled analysis [512]. Observation was most effective in men aged 65–75 years with low-risk PCa [513].

Co-morbidity is as important as age in predicting life expectancy in men with PCa. Increasing co-morbidity greatly increases the risk of dying from non-PCa-related causes and for those men with a short life expectancy. In an analysis of 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI score ≥ 2 had died from competing causes at 10 years follow-up regardless of their age at time of diagnosis. Tumour aggressiveness had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of cancer. Men with a CCI score ≤ 1 had a low risk of death at 10 years, especially for well- or moderately-differentiated lesions [489]. This highlights the importance of assessing co-morbidity before considering a biopsy.

In screen-detected localised PCa the lead-time bias is likely to be greater. Mortality from untreated screen-detected PCa in patients with ISUP grade 1–2 might be as low as 7% at 15 years follow-up [514]. Consequently, approximately 45% of men with PSA-detected PCa are suitable for close follow-up through a robust surveillance programme. There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and WW (Table 6.1.1).

6.1.1.1 Definitions

Active surveillance aims to avoid unnecessary treatment in men with clinically localised PCa who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [515]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up consisting of PSA testing, clinical examination, MRI imaging and repeat prostate biopsies, with curative treatment being prompted by pre-defined thresholds indicative of potentially life-threatening disease, which is still potentially curable, while considering individual life expectancy.

Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment from the outset, and patients are clinically 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms in order to maintain QoL.

Table 6.1.1: Definitions of active surveillance and watchful waiting [514]

	Active surveillance	**Watchful waiting**
Treatment intent	Curative	Palliative
Follow-up	Pre-defined schedule	Patient-specific
Assessment/markers used	DRE, PSA, MRI at recruitment, re-biopsy	Not pre-defined, but dependent on development of symptoms of progression
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
Eligible patients	Mostly low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; MRI = magnetic resonance imaging.

6.1.1.2 Active surveillance

No formal RCT is available comparing this modality to standard treatment. The ProtecT trial is discussed later as it is not a formal AS strategy but rather active monitoring (AM), which is a significantly less stringent surveillance strategy in terms of clinical follow-up, imaging and repeat biopsies [516].

Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a systematic review [517]. More recently, the largest prospective series of men with low-risk PCa managed by AS was published [518]. Table 6.1.2 summarises the results of selective AS cohorts. It is clear that the long-term OS and CSS of patients on AS are extremely good. However, more than one-third of patients are 'reclassified' during follow-up, most of whom undergo curative treatment due to disease upgrading, increase in disease extent, disease stage, progression or patient preference. There is considerable variation and heterogeneity between studies regarding patient selection and eligibility, follow-up policies (including frequency and type of imaging such as MRI imaging, type and frequency of repeat prostate biopsies, such as MRI-targeted biopsies or transperineal template biopsies, use of PSA kinetics and density, and frequency of clinical follow-up), when active treatment should be instigated (i.e. reclassification criteria) and which outcome measures should be prioritised [515]. These will be discussed further in section 6.2.1.

Table 6.1.2: Active surveillance in screening-detected prostate cancer
(large cohorts with longer-term follow-up)

Studies	N	Median FU (mo)	pT3 in RP patients*	10-year OS (%)	10-year CSS (%)
Van As, *et al.* 2008 [519]	326	22	8/18 (44%)	98	100
Carter, *et al.* 2007 [520]	407	41	10/49 (20%)	98	100
Adamy, *et al.* 2011 [521]	533-1,000	48	4/24 (17%)	90	99
Soloway, *et al.* 2010 [522]	99	45	0/2	100	100
Roemeling, *et al.* 2007 [523]	278	41	-	89	100
Khatami, *et al.* 2007 [524]	270	63	-	n.r.	100
Klotz, *et al.* 2015 [525]	993	77	-	85	98.1
Tosoian, *et al.* 2015 [518]	1,818	60	-	93	99.9
Total	**4,724-5,191**	**46.5**	**-**	**93**	**99**

** Patients receiving active therapy following initial active surveillance.*
CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; n.r. = not reported; OS = overall survival; RP = radical prostatectomy.

6.1.1.3 Watchful Waiting

6.1.1.3.1 Outcome of watchful waiting compared with active treatment

The SPCG-4 study was a RCT from the pre-PSA era, randomising patients to either WW or RP (Table 6.1.3) [526]. The study found RP to provide superior CSS, OS and PFS compared to WW at a median follow-up of 23.6 years (range 3 weeks–28 years). However, the benefit in favour of RP over WW was only apparent after 10 years. The PIVOT trial was a RCT conducted in the early PSA era and made a similar comparison between RP vs. WW in 731 men (50% with non-palpable disease) but in contrast to the SPCG-4, it found little, to no, benefit of RP (cumulative incidence of all-cause death, RP vs. observation: 68% vs. 73%; RR: 0.92, 95% CI: 0.84–1.01) within a median follow-up period of 18.6 years (interquartile range, 16.6 to 20 years) [527]. Exploratory subgroup analysis showed that the borderline benefit from RP was most marked for intermediate-risk disease (RR: 0.84, 95% CI: 0.73–0.98) but there was no benefit in patients with low- or high-risk disease. Overall, no adverse effects on health-related QoL (HRQoL) and psychological well-being was apparent in the first 5 years [528]. However, one of the criticisms of the PIVOT trial is the relatively high overall mortality rate in the WW group compared with more contemporary series. A Cochrane review performed a pooled analysis of RCTs comparing RP vs. WW [529]. Three studies were included (including the Veteran's Administration Cooperative Urological Research Group [VACURG] study which was conducted in the pre-PSA era [530], SPCG-4 and PIVOT). The authors found RP had lower overall mortality (HR: 0.79, 95% CI: 0.70–0.90) and lower cancer-specific mortality (HR: 0.57, 95% CI: 0.44–0.73) compared with WW at 29 years' follow-up. Radical prostatectomy also had lower risk of progression (HR: 0.43, 95% CI: 0.35–0.54) and lower risk of metastatic disease (HR: 0.56, 95% CI: 0.46–0.70). However, RP was associated with higher rates of urinary incontinence (RR: 3.97, 95% CI 2.34–6.74) and erectile dysfunction (ED) (RR: 2.67, 95% CI: 1.63–4.38).

The overall evidence indicates that for men with asymptomatic, clinically localised PCa and with a life expectancy of < 10 years based on co-morbidities and/or age, the oncological advantages of active treatment over WW are unlikely to be relevant to them. Consequently, WW should be adopted for such patients.

Table 6.1.3: Outcome of SPCG-4 at a median follow-up of 23.6 years [526]

	RP (n = 348) (%)	Watchful waiting (n = 348) (%)	Relative risk (95% CI)	p-value
Disease-specific mortality	19.6	31.3	0.55 (0.41–0.74)	< 0.001
Overall mortality	71.9	83.8	0.74 (0.62–0.87)	< 0.001
Metastatic progression	26.6	43.3	0.54 (0.42–0.70)	< 0.001

CI = confidence interval; RP = radical prostatectomy.

6.1.1.4 The ProtecT trial

The ProtecT trial randomised 1,643 patients into three arms: active treatment with either RP or EBRT, and active monitoring (AM) [525]. In this AM schedule patients with a PSA rise of more than 50% in 12 months underwent a repeat biopsy, but none had systematic repeat biopsies. Fifty-six percent of patients had low-risk disease, with 90% having a PSA < 10 ng/mL, 77% ISUP grade 1 (20% ISUP grade 2–3), and 76% T1c,

while the other patients had mainly intermediate-risk disease. After 10 years of follow-up, CSS was the same between those actively treated and those on AM (99% and 98.8%, respectively), as was the OS. Only metastatic progression differed (6% in the AM group as compared to 2.6% in the treated group). The key finding was that AM was as effective as active treatment at 10 years, at a cost of increased progression and double the metastatic risk. Metastases remained rare (6%), but more frequent than seen with AS protocols; probably driven by differences in intensity of monitoring and patient selection. It is important to note that the AM arm in ProtecT represented an intermediate approach between contemporary AS protocols and WW in terms of a monitoring strategy based almost entirely on PSA measurements alone; there was no use of MRI scan, either at recruitment or during the monitoring period, nor were there any protocol-mandated repeat prostate biopsies at regular intervals. In addition, approximately 40% of randomised patients had intermediate-risk disease. Nevertheless, the ProtecT study has reinforced the role of deferred active treatment (i.e. either AS or some form of initial AM) as a feasible alternative to active curative interventions in patients with low-grade and low-stage disease. Beyond 10 years, no data is available, as yet, although AS is likely to give more reassurance especially in younger men, based on more accurate risk stratification at recruitment and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must be evaluated before considering any active treatment in low-risk patients and in those with up to 10 years' individual life expectancy [531].

Recently, Bryant *et al*., performed a comprehensive characterisation of the ProtecT study cohort, stratifying patients at baseline according to risk of progression using clinical stage, grade at diagnosis and PSA level [531]. Additionally, detailed clinico-pathological information on participants who received RP were analysed. The authors aimed to test the hypothesis that the clinico-pathological features of participants with disease progression differed from those with stable disease in order to identify prognostic markers. The results showed that out of all patients who had been randomised (n = 1,643), 34% (n = 505) had intermediate- or high-risk disease, and 66% (n = 973) had low-risk disease. Out of all patients who had received AM, RP or RT within 12 months of randomisation (n = 1,607), at a median follow-up of 10 years, 12% of patients (n = 198) developed progression, of which 72% (n = 142) had undergone AM. Treatment received, age (65–69 vs. 50–64 years), PSA, GG at diagnosis, cT stage, risk group, number of PCa-involved biopsy cores, maximum length of tumour (median 5.0 vs. 3.0 mm), aggregate length of tumour (median 8.0 vs. 4.0 mm), and presence of perineural invasion were each associated with increased risk of disease progression ($p < 0.001$ for each). However, these factors could not reliably predict progression in individuals. Notably, 53% (n = 105) of patients who progressed had biopsy GG 1 disease, although, conversely, none of the participants who received RP and subsequently progressed had pathological GG 1 tumours. This discrepancy can be explained by inadequate sampling by PSA testing and 10-core TRUS-guided biopsies.

*6.1.2 **Radical prostatectomy***

6.1.2.1 Introduction

The goal of RP by any approach is the eradication of cancer while, whenever possible, preserving pelvic organ function [532]. The procedure involves removing the entire prostate with its capsule intact and SVs, followed by vesico-urethral anastomosis. Surgical approaches have expanded from perineal and retropubic open approaches to laparoscopic and robotic-assisted techniques; anastomoses have evolved from Vest approximation sutures to continuous suture watertight anastomoses under direct vision and mapping of the anatomy of the dorsal venous complex (DVC) and cavernous nerves has led to excellent visualisation and potential for preservation of erectile function [533]. The main results from multi-centre RCTs involving RP are summarised in Table 6.1.4.

Table 6.1.4: Oncological results of radical prostatectomy in organ-confined disease in RCTs

Study	Acronym	Population	Treatment period	Median FU (mo)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [526]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk and Intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [534]	PIVOT	Early years of PSA testing	1994-2002	152	Low risk Intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2016 [516]	ProtecT	Screened population	1999-2009	120	Mainly low- and intermediate risk	99 (at 10 yr.)

CSS = cancer-specific survival; FU = follow-up; mo = months; PSA = prostate-specific antigen; yr. = year.

6.1.2.2 Pre-operative preparation

6.1.2.2.1 Pre-operative patient education

As before any surgery appropriate education and patient consent is mandatory prior to RP. Peri-operative education has been shown to improve long-term patient satisfaction following RP [535]. Augmentation of standard verbal and written educational materials such as use of interactive multimedia tools [536, 537] and pre-operative patient-specific 3D printed prostate models has been shown to improve patient understanding and satisfaction and should be considered to optimise patient-centred care [538].

6.1.2.2.2 Pre-operative pelvic floor exercises

Although many patients who have undergone RP will experience a return to urinary continence [539], temporary urinary incontinence is common early after surgery, reducing QoL. Pre-operative pelvic floor exercises (PFE) with, or without, biofeedback have been used with the aim of reducing this early post-operative incontinence. A systematic review and meta-analysis of the effect of pre-RP PFE on post-operative urinary incontinence showed a significant improvement in incontinence rates at 3 months post-operatively with an OR of 0.64 ($p = 0.005$), but not at 1 month or 6 months [540]. Pre-operative PFE may therefore provide some benefit, however the analysis was hampered by the variety of PFE regimens and a lack of consensus on the definition of incontinence.

6.1.2.2.3 Prophylactic antibiotics

Prophylactic antibiotics should be used; however, no high-level evidence is available to recommend specific prophylactic antibiotics prior to RP (See EAU Urological Infections Guidelines [541]). In addition, as the susceptibility of bacterial pathogens and antibiotic availability varies worldwide, any use of prophylactic antibiotics should adhere to local guidelines.

6.1.2.2.4 Neoadjuvant androgen deprivation therapy

Several RCTs have analysed the impact of neoadjuvant ADT before RP, most of these using a 3-month period. The main findings were summarised in a Cochrane review [542]. Neoadjuvant ADT is associated with a decreased rate of pT3 (downstaging), decreased positive margins, and a lower incidence of positive LNs. These benefits are greater with increased treatment duration (up to 8 months). However, since neither the PSA relapse-free survival nor CSS were shown to improve, neoadjuvant ADT should not be considered as standard clinical practice. One recent RCT compared neoadjuvant luteinising hormone-releasing hormone (LHRH) alone vs. LHRH plus abiraterone acetate plus prednisone (AAP) prior to RP in 65 localised high-risk PCa patients [543]. Patients in the combination arm were found to have both significantly lower tumour volume and significantly lower BCR at > 4 years follow-up ($p = 0.0014$). A pooled analysis of 3 RCTs, including 117 patients and assessing the impact of intense neoadjuvant deprivation therapy has reported a complete pathological response rate of 9.4%, with improved BCR outcomes in complete responders [544]. Further supportive evidence is required before recommending combination neoadjuvant therapy including abiraterone prior to RP. Another RCT (CALGB 90203), comparing RP alone to RP with neoadjuvant chemo-hormonal therapy (CHT) including docetaxel for clinically high-risk localised PCa did not meet the study's primary endpoint of biochemical PFS at 3 years post-operatively, due to contamination with early salvage RT. As a result, CHT is not currently recommended unless longer-term data show a survival benefit using clinical endpoints [545].

6.1.2.3 Surgical techniques

Prostatectomy can be performed by open-, laparoscopic- or robot-assisted (RARP) approaches. The initial open technique of RP described by Young in 1904 was via the perineum [533] but suffered from a lack of access to pelvic LNs. If lymphadenectomy is required during perineal RP it must be done via a separate open retropubic (RRP) or laparoscopic approach. The open retropubic approach was popularised by Walsh in 1982 following his anatomical description of the DVC, enabling its early control and of the cavernous nerves, permitting a bilateral nerve-sparing procedure [546]. This led to the demise in popularity of perineal RP and eventually to the first laparoscopic RP reported in 1997 using retropubic principles, but performed transperitoneally [547]. The initial 9 cases averaged 9.4 hours, an indication of the significant technical and ergonomic difficulties of the technique. Most recently, RARP was introduced using the da Vinci Surgical System® by Binder in 2002 [548]. This technology combined the minimally-invasive advantages of laparoscopic RP with improved surgeon ergonomics and greater technical ease of suture reconstruction of the vesico-urethral anastomosis and has now become the preferred minimally-invasive approach, when available.

In a randomised phase III trial, RARP was shown to have reduced admission times and blood loss, but not earlier (12 weeks) functional or oncological outcomes compared to open RP [549]. An updated analysis with follow-up at 24 months did not reveal any significant differences in functional outcomes between the approaches [550]. Increased surgical experience has lowered the complication rates of RP and improved

cancer cure [510-513]. Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, can improve cancer control with RP [551-553]. There is a lack of studies comparing the different surgical modalities for these longer-term outcomes [509, 528, 534, 554]. A systematic review and meta-analysis of non-RCTs demonstrated that RARP had lower peri-operative morbidity and a reduced risk of positive surgical margins compared with laparoscopic prostatectomy (LRP), although there was considerable methodological uncertainty [555]. There was no evidence of differences in urinary incontinence at 12 months and there was insufficient evidence to draw conclusions based on differences in cancer-related, patient-driven or ED outcomes. Another systematic review and meta-analysis included two small RCTs comparing RARP vs. LRP [556]. The results suggested higher rates of return of erectile function (RR: 1.51, 95% CI: 1.19–1.92) and return to continence function (RR: 1.14, 95% CI: 1.04–1.24) in the RARP group. However, a Cochrane review comparing either RARP or LRP vs. open RP included two RCTs and found no significant differences between the comparisons for oncological-, urinary- and sexual function outcomes, although RARP and LRP both resulted in statistically significant improvements in duration of hospital stay and blood transfusion rates over open RP [557]. Therefore, no surgical approach can be recommended over another.

Outcome after prostatectomy has been shown to be dependent on both surgeon [558] as well as hospital volume [559]. Although various volume criteria have been set worldwide, the level of evidence is insufficient to pinpoint a specific lower volume limit.

6.1.2.3.1 Robotic anterior versus Retzius-sparing dissection

Robot-assisted RP has typically been performed via the anterior approach, first dropping the bladder to expose the space of Retzius. However, the posterior approach (Retzius-sparing [RS-RARP]) has been used to minimise injury to support structures surrounding the prostate.

Galfano *et al.*, first described RS-RARP in 2010 [560]. This approach commences dissection posteriorly at the pouch of Douglas, first dissecting the SVs and progressing caudally behind the prostate. All of the anterior support structures are avoided, giving rise to the hypothetical mechanism for improved early post-operative continence. Retzius-sparing-RARP thus offers the same potential advantage as the open perineal approach, but without disturbance of the perineal musculature.

Retzius-sparing-RARP has been recently investigated in RCTs leading to four systematic reviews and meta-analyses [561-563] including a 2020 Cochrane systematic review [564] and a large propensity score matched analysis [565]. The Cochrane review used the most rigorous methodology and analysed 5 RCTs with 502 patients. It found with moderate certainty that RS-RARP improved continence at 1 week post catheter removal compared to standard RARP (RR: 1.74). Continence may also be improved at 3 months post-operatively (RR: 1.33), but this was based on low-certainty data. Continence outcomes appeared to equalise by 12 months (RR: 1.01). These findings matched those of the other systematic reviews. However, a significant concern was that RS-RARP appears to increase the risk of positive margins (RR: 1.95) but this was also low-certainty evidence. A single-surgeon propensity score matched analysis of 1,863 patients reached the same conclusion as the systematic reviews regarding earlier return to continence but did not show data on margin status [565].

Based on these data, recommendations cannot be made for one technique over another. However, the trade-offs between the risks of a positive margin vs. earlier continence recovery should be discussed with prospective patients. Furthermore, no high-level evidence is available on high-risk disease with some concerns that RS-RARP may confer an increased positive margin rate based on pT3 results. In addition, RS-RARP may be more technically challenging in various scenarios such as anterior tumours, post-TURP, a grossly enlarged gland, or a bulky median lobe [566].

6.1.2.3.2 Pelvic lymph node dissection

A systematic review demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [567]. Moreover, two RCTs have failed to show a benefit of an extended approach vs. a limited PLND on early oncologic outcomes [568, 569]. However, it is generally accepted that eLND provides important information for staging and prognosis which cannot be matched by any other currently available procedure [567].

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. With this template, 94% of patients are correctly staged [570].

The individual risk of patients harbouring positive LNs can be estimated based on validated nomograms. The Briganti nomogram [426, 427], the Roach formula [571] or the Partin and MSKCC nomograms [572] have

shown similar diagnostic accuracy in predicting LN invasion. These nomograms have all been developed in the pre-MRI setting based on systematic random biopsy. A risk of nodal metastases over 5% can be used to identify candidates for nodal sampling by eLND during RP [573-575].

An updated nomogram has been externally validated in men diagnosed based on MRI followed by MRI-targeted biopsy [427]. Based on this nomogram patients can be spared an ePLND if their risk of nodal involvement is less than 7%; which would result in missing only 1.5% of patients with nodal invasion [427, 430]. This 7% cut-off is comparable to the 5% cut-off of the Briganti nomogram in patients diagnosed by systematic random biopsy alone. Therefore, this novel nomogram and a 7% threshold should be used after MRI-targeted biopsy to identify candidates for eLND [429].

6.1.2.3.3 Sentinel node biopsy analysis

The rationale for a sentinel node biopsy (SNB) is based on the concept that a sentinel node is the first to be involved by migrating tumour cells. Therefore, when this node is negative it is possible to avoid an ePLND. There is heterogeneity and variation in techniques in relation to SNB (e.g. the optimal tracer) but a multidisciplinary collaborative endeavour attempted to standardise definitions, thresholds and strategies in relation to techniques of SNB using consensus methods [576].

Intraprostatic injections of indocyanine green (ICG) have been used to visualise prostate-related LNs during lymphadenectomy. In a randomised comparison, Harke *et al*., found more cancer containing LNs in men that underwent a LN dissection guided by ICG but no difference in BCR at 22.9-month follow-up [577]. A systematic review showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at eLND [578]. However, there is still insufficient high-quality evidence supporting oncological effectiveness of SNB for nodal staging. Sentinel node biopsy is therefore still considered as an experimental nodal staging procedure.

6.1.2.3.4 Prostatic anterior fat pad dissection and histologic analysis

Several multi-centre and large single-centre series have shown the presence of lymphoid tissue within the fat pad anterior to the endopelvic fascia; the prostatic anterior fat pad (PAFP) [579-585]. This lymphoid tissue is present in 5.5–10.6% of cases and contains metastatic PCa in up to 1.3% of intermediate- and high-risk patients.

When positive, the PAFP is often the only site of LN metastasis. The PAFP is therefore a rare but recognised route of spread of disease. Unlike PLND, there is no morbidity associated with removal of the PAFP. The PAFP is always removed at RP for exposure of the endopelvic fascia and should be sent for histologic analysis as per all removed tissue.

6.1.2.3.5 Management of the dorsal venous complex

Since the description of the anatomical open RP by Walsh and Donker in the 1980s, various methods of controlling bleeding from the DVC have been proposed to optimise visualisation [546]. In the open setting, blood loss and transfusion rates have been found to be significantly reduced when ligating the DVC prior to transection [586]. However, concerns have been raised regarding the effect of prior DVC ligation on apical margin positivity and continence recovery due to the proximity of the DVC to both the prostatic apex and the urethral sphincter muscle fibres. In the robotic-assisted laparoscopic technique, due to the increased pressure of pneumoperitoneum, whether prior DVC ligation was used or not, blood loss was not found to be significantly different in one study [587]. In another study, mean blood loss was significantly less with prior DVC ligation (184 vs. 176 mL, $p = 0.033$), however it is debatable whether this was clinically significant [588]. The positive apical margin rate was not different, however, the latter study showed earlier return to full continence at 5 months post-operatively in the no prior DVC ligation group (61% vs. 40%, $p < 0.01$).

Ligation of the DVC can be performed with standard suture or using a vascular stapler. One study found significantly reduced blood loss (494 mL vs. 288 mL) and improved apical margin status (13% vs. 2%) when using the stapler [589].

Given the relatively small differences in outcomes, the surgeon's choice to ligate prior to transection or not, or whether to use sutures or a stapler, will depend on their familiarity with the technique and the equipment available.

6.1.2.3.6 Nerve-sparing surgery

During prostatectomy, preservation of the neurovascular bundles with parasympathetic nerve branches of the pelvic plexus may spare erectile function [590, 591].

Although age and pre-operative function may remain the most important predictors for post-operative erectile function, nerve-sparing has also been associated with improved continence outcomes and

may therefore still be relevant for men with poor erectile function [592, 593]. The association with continence may be mainly due to the dissection technique used during nerve-sparing surgery, and not due to the preservation of the nerve bundles themselves [592].

Extra-, inter-, and intra-fascial dissection planes can be planned, with those closer to the prostate and performed bilaterally associated with superior (early) functional outcomes [594-597]. Furthermore, many different techniques are propagated such as retrograde approach after anterior release (vs. antegrade), and athermal and traction-free handling of bundles [598-600]. Nerve-sparing does not compromise cancer control if patients are carefully selected depending on tumour location, size and grade [601-603].

6.1.2.3.7 Lymph-node-positive patients during radical prostatectomy

Although no RCTs are available, data from prospective cohort studies comparing survival of pN+ patients (as defined following pathological examination after RP) support that RP may have a survival benefit over abandonment of RP in node-positive cases [604]. As a consequence there is no role for performing frozen section of suspicious LNs.

6.1.2.3.8 Removal of seminal vesicles

The more aggressive forms of PCa may spread directly into the SVs. For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen [605]. However, in some patients the tips of the SVs can be challenging to dissect free. Furthermore, the cavernous nerves run past the SV tips such that indiscriminate dissection of the SV tips could potentially lead to ED [606]. However, a RCT comparing nerve-sparing RP with and without a SV-sparing approach found no difference in margin status, PSA recurrence, continence or erectile function outcomes. Another study of 71 consecutive RPs showed no cancer in any of the distal 1 cm of SVs, even in 12 patients with SV invasion [607]. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement.

6.1.2.3.9 Techniques of vesico-urethral anastomosis

Following prostate removal, the bladder neck is anastomosed to the membranous urethra. The objective is to create a precisely aligned, watertight, tension-free, and stricture-free anastomosis that preserves the integrity of the intrinsic sphincter mechanism. Several methods have been described, based on the direct or indirect approach, the type of suture (i.e. barbed vs. non-barbed/monofilament), and variation in suturing technique (e.g., continuous vs. interrupted, or single-needle vs. double-needle running suture). The direct vesico-urethral anastomosis, which involves the construction of a primary end-to-end inter-mucosal anastomosis of the bladder neck to the membranous urethra by using 6 interrupted sutures placed circumferentially, has become the standard method of reconstruction for open RP [608].

The development of laparoscopic- and robotic-assisted techniques to perform RP have facilitated the introduction of new suturing techniques for the anastomosis. A systematic review and meta-analysis compared unidirectional barbed suture vs. conventional non-barbed suture for vesico-urethral anastomosis during robotic-assisted laparoscopic prostatectomy (RALP) [609]. The review included 3 RCTs and found significantly reduced anastomosis time, operative time and posterior reconstruction time in favour of the unidirectional barbed suture technique, but there were no differences in post-operative leak rate, length of catheterisation and continence rate. However, no definitive conclusions could be drawn due to the relatively low quality of the data. In regard to suturing technique, a systematic review and meta-analysis compared continuous vs. interrupted suturing for vesico-urethral anastomosis during RP [610]. The study included only one RCT with 60 patients [611]. Although the review found slight advantages for continuous suturing over interrupted suturing in terms of catheterisation time, anastomosis time and rate of extravasation, the overall quality of evidence was low and no clear recommendations were possible. A recent RCT [612] compared the technique of suturing using a single absorbable running suture vs. a double-needle single-knot running suture (i.e. Van Velthoven technique) in laparoscopic RP [613]. The study found slightly reduced anastomosis time with the single running suture technique, but anastomotic leak, stricture, and continence rates were similar.

Overall, although there are a variety of approaches, methods and techniques for performing the vesico-urethral anastomosis, no clear recommendations are possible due to the lack of high-certainty evidence. In practice, the chosen method should be based on surgeon experience and individual preference [608-619].

6.1.2.3.10 Bladder neck management

Bladder neck mucosal eversion

Some surgeons perform mucosal eversion of the bladder neck as its own step in open RP with the aim of securing a mucosa-to-mucosa vesico-urethral anastomosis and avoiding anastomotic stricture. Whilst bringing bladder and urethral mucosa together by the everted bladder mucosa covering the bladder muscle layer, this

step may actually delay healing of the muscle layers. An alternative is to simply ensure bladder mucosa is included in the full thickness anastomotic sutures. A non-randomised study of 211 patients with and without bladder neck mucosal eversion showed no significant difference in anastomotic stricture rate [620]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [621].

Bladder neck preservation

Whilst the majority of urinary continence is maintained by the external urethral sphincter at the membranous urethra (see below), a minor component is contributed by the internal lissosphincter at the bladder neck [622]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. A RCT assessing continence recovery at 12 months and 4 years showed improved objective and subjective urinary continence in both the short- and long term without any adverse effect on oncological outcome [623]. These findings were confirmed by a systematic review [624]. However, concern remains regarding margin status for cancers located at the prostate base.

A systematic review addressing site-specific margin status found a mean base-specific positive margin rate of 4.9% with bladder neck preservation vs. only 1.9% without [622]. This study was inconclusive, but it would be sensible to exercise caution when considering bladder neck preservation if significant cancer is known to be at the prostate base. Bladder neck preservation should be performed routinely when the cancer is distant from the base. However, bladder neck preservation cannot be performed in the presence of a large median lobe or a previous TURP.

6.1.2.3.11 Urethral length preservation

The membranous urethra sits immediately distal to the prostatic apex and is chiefly responsible, along with its surrounding pelvic floor support structures, for urinary continence. It consists of the external rhabdosphincter which surrounds an inner layer of smooth muscle. Using pre-operative MRI, the length of membranous urethra has been shown to vary widely. A systematic review and meta-analysis has found that every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post-RP [625]. Therefore, it is likely that preservation of as much urethral length as possible during RP will maximise the chance of early return to continence. It may also be useful to measure urethral length pre-operatively to facilitate counselling of patients on their relative likelihood of early post-operative continence.

6.1.2.3.12 Cystography prior to catheter removal

Cystography may be used prior to catheter removal to check for a substantial anastomotic leak. If such a leak is found, catheter removal may then be deferred to allow further healing and sealing of the anastomosis. However, small comparative studies suggest that a cystogram to assess anastomotic leakage is not indicated as SOC before catheter removal 8 to 10 days after surgery [626]. If a cystogram is used, men with LUTS, large prostates, previous TURP or bladder neck reconstruction, may benefit as these factors have been associated with leakage [627, 628]. Contrast-enhanced transrectal US is an alternative [629].

6.1.2.3.13 Urinary catheter

A urinary catheter is routinely placed during RP to enable bladder rest and drainage of urine while the vesicourethral anastomosis heals. Compared to a traditional catheter duration of around 1 week, some centres remove the transurethral catheter early (post-operative day 2–3), usually after thorough anastomosis with posterior reconstruction or in patients selected peri-operatively on the basis of anastomosis quality [630-633]. No higher complication rates were found. Although shorter catheterisation has been associated with more favourable short-term functional outcomes, no differences in long-term function were found [634]. One RCT has shown no difference in rate of UTI following indwelling catheter (IDC) removal whether prophylactic ciprofloxacin was given prior to IDC removal or not, suggesting antibiotics should not be given at catheter removal [635].

As an alternative to transurethral catheterisation, suprapubic catheter insertion during RP has been suggested. Some reports suggest less bother regarding post-operative hygiene and pain [636-640], while others did not find any differences [641, 642]. No impact on long-term functional outcomes were seen.

6.1.2.3.14 Use of a pelvic drain

A pelvic drain has traditionally been used in RP for potential drainage of urine leaking from the vesico-urethral anastomosis, blood, or lymphatic fluid when a PLND has been performed. Two RCTs in the robotic-assisted laparoscopic setting have been performed [643, 644]. Patients with urine leak at intra-operative anastomosis watertight testing were excluded. Both trials showed non-inferiority in complication rates when no drain was used. When the anastomosis is found to be watertight intra-operatively, it is reasonable to avoid inserting a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

6.1.2.4 Acute and chronic complications of surgery

Post-operative incontinence and ED are common problems following surgery for PCa. A key consideration is whether these problems are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [555, 645-648], and can be compared with contemporaneous reports after radical RRP [649]. A prospective controlled non-RCT of patients undergoing RP in 14 centres using RALP or RRP showed that 12 months after RALP, 21.3% of patients were incontinent, as were 20.2% after RRP (adjusted OR: 1.08, 95% CI: 0.87–1.34) [650]. Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66–0.98) [650].

A systematic review and meta-analysis of unplanned hospital visits and re-admissions post-RP analysed 60 studies with over 400,000 patients over a 20-year period up to 2020. It found an emergency room visit rate of 12% and a hospital re-admission rate of 4% at 30 days post-operatively [651].

A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at 2 years [549]. Urinary function scores did not differ significantly between RRP vs. RALP at 6 and 12 weeks post-surgery (74–50 vs. 71–10, p = 0.09; 83–80 vs. 82–50, p = 0.48), with comparable outcomes for sexual function scores (30–70 vs. 32–70, p = 0.45; 35–00 vs. 38–90, p = 0.18). In the RRP group 14 (9%) patients had post-operative complications vs. 6 (4%) in the RALP group. The intra-and peri-operative complications of retropubic RP and RALP are listed in Table 6.1.5. The early use of phosphodiesterase-5 (PDE5) inhibitors in penile rehabilitation remains controversial resulting in a lack of clear recommendations (see Section 8.3.2.1).

6.1.2.4.1 Effect of anterior and posterior reconstruction on continence

Preservation of integrity of the external urethral sphincter is critical for continence post-RP. Less clear is the effect of reconstruction of surrounding support structures to return to continence. Several small RCTs have been conducted, however, pooling analyses is hampered by variation in the definitions of incontinence and surgical approach, such as open vs. robotic and intraperitoneal vs. extraperitoneal. In addition, techniques used to perform both anterior suspension or reconstruction and posterior reconstruction are varied. For example, anterior suspension is performed either through periosteum of the pubis or the combination of ligated DVC and puboprostatic ligaments (PPL). Posterior reconstruction from rhabdosphincter is described to either Denonvilliers fascia posterior to bladder or to posterior bladder wall itself.

Two trials assessing posterior reconstruction in RALRP found no significant improvement in return to continence [652, 653]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to 1 pad per day (median 18 vs. 30 days, p = 0.024) [654]. When combining both anterior and posterior reconstruction, where for anterior reconstruction the PPL were sutured to the anterior bladder neck, another RCT found no improvement compared to a standard anastomosis with no reconstruction [655].

Four RCTs including anterior suspension have also shown conflicting results. Anterior suspension alone through the pubic periosteum, in the setting of extraperitoneal RALRP, showed no advantage [656]. However, when combined with posterior reconstruction in RRP, one RCT showed significant improvement in return to continence at one month (7.1% vs. 26.5%, p = 0.047) and 3 months (15.4% vs. 45.2%, p = 0.016), but not at 6 months (57.9% vs. 65.4%, p = 0.609) [657]. Another anterior plus posterior reconstruction RCT using the Advanced Reconstruction of VesicoUrethral Support (ARVUS) technique and the strict definition of continence of 'no pads', showed statistically significant improvement in continence at 2 weeks (43.8% vs. 11.8%), 4 weeks (62.5% vs. 14.7%), 8 weeks (68.8% vs. 20.6%), 6 months (75% vs. 44.1%) and 12 months (86.7% vs. 61.3%), when compared to standard posterior Rocco reconstruction [658]. Anterior suspension alone through the DVC and PPL combined without posterior construction in the setting of RRP has shown improvement in continence at one month (20% vs. 53%, p = 0.029), 3 months (47% vs. 73%, p = 0.034) and 6 months (83% vs. 100%, p = 0.02), but not at 12 months (97% vs. 100%, p = 0.313) [659]. Together, these results suggest a possible earlier return to continence, but no long-term difference.

As there is conflicting evidence on the effect of anterior and/or posterior reconstruction on return to continence post-RP, no recommendations can be made. However, no studies showed an increase in adverse oncologic outcome or complications with reconstruction.

6.1.2.4.2 Deep venous thrombosis prophylaxis

For EAU Guidelines recommendations on post-RP deep venous thrombosis prophylaxis, please see the Thromboprophylaxis Guidelines Section 3.1.6 [660]. However, these recommendations should be adapted based on national recommendations, when available.

Table 6.1.5: Intra-and peri-operative complications of retropubic RP and RALP (Adapted from [555]**)**

Predicted probability of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep-vein thrombosis	0.6	0.2	1.4
Predicted rates of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IVa	0.6	0.8	2.1
Clavien V	< 0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

6.1.2.4.3 Early complications of extended lymph node dissection

Pelvic eLND increases morbidity in the treatment of PCa [567]. Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event. Other authors have reported more acceptable complication rates [661]. Similar rates of lymphoceles have been observed in RALP series; however, in one subgroup analysis lymphoceles were more common with the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [662, 663]. Briganti *et al*., [664] also showed more complications after extended compared to limited LND. Twenty percent of men suffer a complication of some sort after eLND. Thromboembolic events occur in less than 1% of cases.

6.1.3 ***Radiotherapy***

Intensity-modulated RT (IMRT) or volumetric arc radiation therapy (VMAT) with image-guided RT (IGRT) is currently widely recognised as the best available approach for EBRT.

6.1.3.1 External beam radiation therapy

6.1.3.1.1 Technical aspects

Intensity-modulated EBRT and volumetric arc external-beam RT (VMAT) employ dynamic multileaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. Viani *et al.*, show significantly reduced acute and late grade ≥ 2 genito-urinary (GU) and gastro-intestinal (GI) toxicity in favour of IMRT, while BCR-free rates did not differ significantly when comparing IMRT with three-dimensional conformal radiation therapy (3D-CRT) in a RCT comprising 215 patients [665]. A meta-analysis by Yu *et al.*, (23 studies, 9,556 patients) concluded that IMRT significantly decreases the occurrence of grade 2–4 acute GI toxicity, late GI toxicity and late rectal bleeding, and achieves better PSA relapse-free survival in comparison with 3D-CRT. Intensity-modulated EBRT and 3D-CRT show comparable acute rectal toxicity, late GU toxicity and OS, while IMRT slightly increases the morbidity of acute GU toxicity [666]. Wortel *et al.*, concluded that, as compared to 3D-CRT, image-guided IMRT was associated with significantly reduced late GI toxicity whereas GU toxicities remained comparable (242 IMRT patients vs. 189 3D-CRT patients) [667]. Finally, Zapatero *et al.*, found, based on 733 consecutive patients (295 IMRT vs. 438 3D-CRT), that compared with 3D-CRT, high-dose IMRT/IGRT is associated with a lower rate of late urinary complications despite a higher radiation dose [668]. In conclusion, IMRT plus IGRT remain the SOC for the treatment of PCa.

The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes. Both techniques allow for a more complex distribution of the dose to be delivered and provide concave isodose curves, which are particularly useful as a means of sparing the rectum. Radiotherapy treatment planning for IMRT and VMAT differs from that used in conventional EBRT, requiring a computer system capable of 'inverse planning' and the appropriate physics expertise. Treatment plans must conform to pre-specified dose constraints to critical organs at risk of normal tissue damage and a formal quality assurance process should be routine.

With dose escalation using IMRT/VMAT, organ movement becomes a critical issue in terms of both tumour control and treatment toxicity. Techniques will therefore combine IMRT/VMAT with some form of IGRT (usually gold marker or cone-beam CT), in which organ movement can be visualised and corrected for in real time, although the optimum means (number of applications per week) of achieving this is still unclear [669, 670].

Tomotherapy is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring, analogous to spiral CT scanning.

6.1.3.1.2 Dose escalation

Local control is a critical issue for the outcome of RT of PCa. It has been shown that local failure due to insufficient total dose is prognostic for death from PCa as a second wave of metastases is seen 5 to 10 years later on [671]. Several RCTs have shown that dose escalation (range 74–80 Gy) has a significant impact on 10-year biochemical relapse as well as metastases and disease-specific mortality [672-679]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant HT has varied (see Table 6.1.6). The best evidence of an OS benefit in patients with intermediate- or high-risk PCa, but not with low-risk PCa, derives from a non-randomised but well conducted propensity-matched retrospective analysis of the U.S. National Cancer Database including a total of 42,481 patients [680]. The concept of a focal boost to the dominant intraprostatic lesion in the MRI has been successfully validated in a RCT of 571 intermediate- and high-risk patients [681]. Patients were randomised between 77 Gy in 35 fractions of 2.2 Gy and the same dose plus a focal boost up to 18 Gy. Additional ADT was given to 65% of patients in both arms. However, the duration of the ADT was not reported. With a median follow-up of 72 months there was a moderate improvement of biochemical PFS (primary endpoint) only. No significant difference for late GU- or GI toxicity grade ≥ 2 (23% and 12% vs. 28% and 13%) was documented. For grade ≥ 3 GU-toxicity these numbers were 3.5% and 5.6% ($p > 0.05$). However, longer follow-up is needed to assess late GU-toxicity. Of note, there was a clear decrease in biochemical failure with increasing boost dose, individually given up to 18 Gy. In everyday practice, a minimum dose of > 74 Gy is recommended for EBRT plus HT, with no different recommendations according to the patient's risk group. If IMRT/VMAT and IGRT are used for dose escalation, rates of severe late side effects (> grade 3) for the rectum are 2–3% and for the GU tract 2–5% [674, 677, 682-695].

Table 6.1.6: Randomised trials of dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
MD Anderson study 2011 [679]	301	T1-T3, N0, M0, PSA ≤ 10 ng/mL PSA 10-20 ng/mL PSA > 20 ng/mL	70 vs.78 Gy	15 yr.	DM, DSM, FFF	All patients: 18.9% FFF at 70 Gy 12% FFF at 78 Gy (p = 0.042) 3.4% DM at 70 Gy 1.1% DM at 78 Gy (p = 0.018) 6.2% DSM at 70 Gy 3.2% DSM at 78 Gy (p = 0.043) No difference in OS (p > 0.05)
PROG 95-09 2010 [673]	393	T1b-T2b PSA ≤ 15 ng/mL 75% low-risk pts. Low-risk: T1-2a, PSA < 10 mg/mL, GS ≤ 6 Interm-risk: PSA 10-15 ng/mL or GS 7 or T2b High-risk: GS 8-10	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	8.9 yr.	10-yr. ASTRO BCF	All patients: 32% BF at 70.2 Gy 17% BF at 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF at 70.2 Gy 7% BF at 79.2 Gy (p < 0.0001)
MRC RT01 2014 [678]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	10 yr.	BFS, OS	43% BFS at 64 Gy 55% BFS at 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)

Dutch randomised phase III trial 2014 [677]	664	T1b-T4 143 pts. with (neo) adjuvant HT	68 vs. 78 Gy	110 mo.	Freedom biochemical (Phoenix) and/or clinical failure at 10 yr.	43% FFF at 68 Gy 49% FFF at 78 Gy (p = 0.045)
GETUG 06 2011 [676]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	61 mo.	BCF (ASTRO)	39% BF at 70 Gy 28% BF at 80 Gy
RTOG 0126 2018 [672]	1,532	T1b-T2b ISUP grade 1 + PSA 10-20 ng/mL or ISUP grade 2/3 + PSA < 15 ng/mL	70.2 vs. 79.2 Gy	100 mo.	OS, DM, BCF (ASTRO)	75% OS at 70.2 Gy 76% OS at 79.2 Gy 6% DM at 70.2 Gy 4% DM at 79.2 Gy (p = 0.05) 47% BCF at 70.2 Gy 31% BCF at 79.2 Gy (p < 0.001; Phoenix, p < 0.001)
FLAME Trial [681]	571	EAU risk classification: Intermediate risk (15%) High risk (84%)	77 Gy (35 fx. 2.2 Gy) vs. 77 Gy (35 Fx.) + focal boost (up to 18 Gy) ADT (65% both arms – duration unknown)	72 mo. (median)	BFS (5 yr.) DSM (5 yr.)	BFS: 92% at 77 Gy + boost 85% at 77 Gy (p < 0.001, HR: 0.45) DSM: p = 0.49

BF = biochemical failure; BFS = biochemical progression-free survival; DM = distant metastases; DSM = disease specific mortality; FFF = freedom from biochemical or clinical failure; HT = hormone therapy; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; yr. = year.

6.1.3.1.3 Hypofractionation

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue and slowly proliferating cells are very sensitive to an increased dose per fraction [696]. A meta-analysis of 25 studies including > 14,000 patients concluded that since PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8–2 Gy [697]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at lower cost.

Moderate HFX is defined as RT with 2.5–3.4 Gy/fx. Several studies report on moderate HFX applied in various techniques also including HT in part [698-708]. A systematic review concluded that studies on moderate HFX (2.5–3.4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to support the safety of this therapy but long-term efficacy data are still lacking [707]. These results were confirmed by a recent Cochrane review on moderate HFX for clinically localised PCa [709]. Eleven studies were included (n = 8,278) with a median follow-up of 72 months showing little or no difference in PCa-specific survival (HR: 1.00). Based on 4 studies (n = 3,848), hypofractionation probably makes little or no difference to late radiation GU toxicity (RR: 1.05) or GI toxicity (RR: 1.1), but this conclusion is based on relatively short follow-up, and 10 to 15-year data will be required to confirm these findings [709].

Moderate HFX should only be done by experienced teams using high-quality EBRT using IGRT and IMRT/VMAT and published phase III protocols should be adhered to (see Table 6.1.7 below).

Table 6.1.7: Major phase III randomised trials of moderate hypofractionation for primary treatment

Study/ Author	n	Risk, ISUP grade, or NCCN	ADT	RT Regimen	BED, Gy	Median FU, mo	Outcome
Lee, *et al.* 2016 [702]	550 542	low risk	None	70 Gy/28 fx 73.8 Gy/41 fx	80 69.6	70	**5 yr. DFS 86.3%** (n.s.) **5 yr. DFS 85.3%**
Dearnaley, *et al.* CHHiP 2012 [698] and 2016 [703]	1077/19 fx 1074/20 fx 1065/37 fx	15% low 73% intermediate 12% high	3-6 mo. before and during EBRT	57 Gy/19 fx 60 Gy/20 fx 74 Gy/37 fx	73.3 77.1 74	62	**5 yr. BCDF** **85.9% (19 fx)** **90.6% (20 fx)** **88.3% (37 fx)**

Aluwini, *et al.*, 2016 & De Vries, *et al.*, 2020 [704, 710]	403 392	30% ISUP grade 1 45% ISUP grade 2-3, 25% ISUP grade 4-5	None	64.6 Gy/19 fx 78 Gy/39 fx	90.4 78	89	**8-yr. OS 80.8% vs. 77.6%** (p = 0.17) **8 yr. TF 24.4% vs. 26.3%**
Catton, *et al.* 2017 [706]	608	intermediate risk 53% T1c 46% T2a-c	None	60 Gy/20 fx	77.1	72	**5 yr. BCDF both arms 85%** HR: 0.96 (n.s)
	598	9% ISUP grade 1 63% ISUP grade 2 28% ISUP grade 3		78 Gy/39 fx	78		

ADT = androgen deprivation therapy; BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2 Gy fractions using an α/ß of 1.5 Gy; DFS = disease-free survival; EBRT = external beam radiotherapy; FU = follow-up; fx = fractions; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo. = month; n = number of patients; NCCN = National Comprehensive Cancer Network; n.s. = not significant; TF = treatment failure; yr. = year.

Ultra-HFX has been defined as RT with > 3.4 Gy per fraction [708]. It requires IGRT and stereotactic body RT (SBRT). Table 6.1.8 provides an overview of selected studies. Short-term biochemical control is comparable to conventional fractionation. However, there are concerns about high-grade GU and rectal toxicity and full long-term side effects may not yet be known [707, 711, 712]. In the HYPO-RT-PC randomised trial by Widmark *et al*., (n = 1,200), no difference in failure-free survival was seen for conventional or ultra-HFX but acute grade ≥ 2 GU toxicity was 23% vs. 28% (p = 0.057), favouring conventional fractionation. There were no significant differences in long-term toxicity [713]. A systematic review by Jackson *et al*., included 38 studies with 6,116 patients who received RT with < 10 fractions and ≥ 5 Gy per fraction. Five and 7-year biochemical recurrence-free survival (BRFS) rates were 95.3% and 93.7%, respectively, and estimated late grade ≥ 3 GU and GI toxicity rates were 2.0% and 1.1%, respectively [714]. The authors conclude that there is sufficient evidence to support SBRT as a standard treatment option for localised PCa, even though the median follow-up in this review was only 39 months and it included at least one trial (HYPO-RT-PC) which used 3D-CRT in 80% and IMRT/VMAT in the remainder for ultra-HFX. In their review on SBRT, Cushman and co-workers evaluated 14 trials, including 2,038 patients and concluded that despite a lack of long-term follow-up and the heterogeneity of the available evidence, prostate SBRT affords appropriate biochemical control with few high-grade toxicities [715]. In the Intensity-modulated fractionated RT vs. stereotactic body RT for PCa (PACE-B) trial, acute grade ≥ 2 GU or GI toxicities did not differ significantly between conventional fractionation and ultra-HFX [716]. Adopting planning dose constraints to the penile bulb might minimise ED, especially in younger patients [717].

First results of a small (n = 30) randomised phase-II trial in intermediate-risk PCa of 'ultra-high single dose RT' (SDRT) with 24 Gy compared with an extreme hypofractionated stereotactic body RT regime with 5x9 Gy to the prostate, have been published recently (see Table 6.1.8) [718]. The primary endpoint was toxic effects. With a median follow-up of 48 months SDRT was relatively well tolerated even though there was a trend towards a higher rate of GU side effects after SDRT at all time points. Longer follow-up should be awaited before any conclusion from this approach can be drawn. In conclusion, it seems prudent to restrict extreme HFX to prospective clinical trials and to inform patients on the uncertainties of the long-term outcome.

Table 6.1.8: Selected trials on ultra-hypofractionation for intact localised PCa

Study	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark *et al.* 2019 HYPO-RT-PC [713]	1,200	60	89% intermediate 11% high	78 Gy / 39 fx, 8 w 42.7 Gy / 7 fx, 2.5 w No SBRT	FFS at 5 yr. 84% in both arms

Brand *et al.* 2019 PACE-B [716]	847	variable	8% low 92% intermediate	78 Gy / 39 fx, 8 wk. 36.25 Gy / 5 fx, 1-2 wk. SBRT	Grade ≥ 2 acute GI 12% vs. 10%, p = 0.38 Grade ≥ 2 acute GU 27% vs. 23%, p = 0.16
Greco *et al*., 2021 PROSINT Randomised phase 2 [718]	30	48	100% intermediate	24 Gy (single dose) 45 Gy, 5 fx, daily SBRT No ADT	Primary endpoint: 'toxic effects' Grade 1 late GU: HR: 0.41 (in favour of SBRT) Grade ≥ 2 late GU: HR: 1.07 Grade 1 late GI: HR: 0.37 (in favour of SBRT)

FFS = failure-free survival; FU = follow-up; fx = number fractions; GI = gastro-intestinal toxicity; GU = genito-urinary toxicity; HR = hazard ratio; mo. = months; n = number of patients; TD = total dose; SBRT = stereotactic body radiotherapy; wk. = weeks; yr. = years.

6.1.3.1.4 Neoadjuvant or adjuvant hormone therapy plus radiotherapy

The combination of RT with LHRH ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [719-723] (Table 6.1.9). The main message is that for all intermediate-risk disease a short duration of around 6 months is optimal while a longer one, around 3 years, is needed for high-risk patients, as per NCCN definition (see Section 4.2). The OS impact of adding short-term ADT for favourable intermediate-risk disease, however, remains a matter of debate [91].

A meta-analysis based on individual patient data from two RCTs (RTOG 9413 and Ottawa 0101) has compared neoadjuvant/concomitant vs. adjuvant ADT (without substratifying between favourable- and unfavourable intermediate-risk disease) in conjunction with prostate RT and reported superior PFS with adjuvant ADT [724]. This is an important observation, which should influence future clinical trial design and evaluation of outcomes. However, there are differences between the two trials in patient characteristics, exact scheduling of neoadjuvant +/- concomitant ADT, hormonal preparation, and RT schedule. At present, either neoadjuvant or adjuvant ADT remain acceptable options for patients requiring short-term ADT in conjunction with EBRT.

Table 6.1.9: Selected studies of use and duration of ADT in combination with RT for PCa

Study	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [720]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65–70 Gy	**Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade 2-5**
RTOG 94-13 2007 [725]	T1c–4 N0–1 M0	1,292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	**No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)**
RTOG 86-10 2008 [721]	T2–4 N0–1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65–70 Gy RT	**No significant difference at 10 yr.**

D'Amico AV, *et al.* 2008 [722]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	**Significant benefit that may pertain only to men with no or minimal co-morbidity** (HR: 0.55, 95% CI: 0.34–0.90, p = 0.01)
RTOG 92-02 2008 [726]	T2c–4 N0–1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65–70 Gy	p = 0.73, p = 0.36 **overall; significant benefit** (p = 0.044) (p = 0.0061) **in subset with ISUP grade 4–5**
EORTC 22961 2009 [727]	T1c–2ab N1 M0, T2c–4 N0–1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70 Gy 3D-CRT	**Better result with 3 yr. treatment than with 6 mo.** (3.8% improvement in survival at 5 yr.)
EORTC 22863 2010 [719]	T1–2 poorly differentiated and M0, or T3–4 N0–1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70 Gy RT	**Significant benefit at 10 yr. for combined treatment** (HR: 0.60, 95% CI: 0.45–0.80, p = 0.0004).
TROG 96-01 2011 [723]	T2b–4 N0 M0	802	Neoadjuvant ADT Duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	**No significant difference in OS reported; benefit in PCa-specific survival** (HR: 0.56, 95% CI: 0.32–0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65–1.08, p = 0.18)
RTOG 99-10 2015 [728]	intermediate risk 94% T1–T2, 6% T3–4	1,579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk.	70.2 Gy 2D/3D	**67 vs. 68%,** p = 0.62, confirms 8 + 8 wk. LHRH as a standard

ADT = androgen deprivation therapy; CI = confidence interval; EBRT = external beam radiotherapy in standard fractionation; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; wk = week; yr. = year.

The question of the added value of EBRT combined with ADT has been clarified by 3 RCTs. All showed a clear benefit of adding EBRT to long-term ADT (see Table 6.1.10).

Table 6.1.10: Selected studies of ADT in combination with, or without, RT for PCa

Study	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [729]	T1b–2 WHO Grade 1–3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. plus continuous flutamide	70 Gy 3D-CRT vs. no RT	34% (95% CI: 29–39%) vs. 17% (95% CI: 13–22% CSM at 12 (15) yr. favouring combined treatment (p < 0.0001 for 15-yr. results) NCIC CTG PR.3/MRC
PRO7/NCIC 2011 [730] and 2015 [731]	T3–4 (88%), PSA > 20 ng/mL (64%), ISUP grade 4–5 (36%) N0 M0	1,205	ADT ± EBRT	Continuous LHRH agonist	65–70 Gy 3D-CRT vs. no RT	10-yr. OS = 49% vs. 55% favouring combined treatment HR: 0.7, p < 0.001)
Sargos, *et al.* 2020 [732]	T3–4 N0 M0	273	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr. OS 71.4% vs. 71.5%

ADT = androgen deprivation therapy; CSM = cancer-specific mortality; EBRT = external beam radiotherapy; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RT = radiotherapy; 3D-CRT = three-dimensional conformal radiotherapy.

6.1.3.1.5 Combined dose-escalated radiotherapy and androgen-deprivation therapy

Zelefsky *et al.*, reported a retrospective analysis comprising 571 patients with low-risk PCa; 1,074 with intermediate-risk PCa and 906 with high-risk PCa. Three-dimensional conformal RT or IMRT were administered [733]. The prostate dose ranged from 64.8 to 86.4 Gy; doses beyond 81 Gy were delivered during the last 10 years of the study using image-guided IMRT. Complete androgen blockade was administered at the discretion of the treating physician to 623 high-risk (69%), 456 intermediate-risk (42%) and 170 low-risk (30%) PCa patients. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before RT. The 10-year biochemical disease-free rate was significantly improved by dose escalation: above 75.6 Gy in low-risk, and above 81 Gy for the intermediate- and high-risk groups. It was also improved by adding 6 months of ADT in intermediate- and high-risk patients. In the multivariate analysis, neither the dose > 81 Gy, nor adding ADT, influenced OS. Four RCTs have shown that the benefits of ADT are independent of dose escalation, and that the use of ADT would not compensate for a lower RT dose:

1. The GICOR study shows a better biochemical DFS in high-risk patients for 3D-CRT radiation dose > 72 Gy when combined with long-term ADT [687].
2. DART01/05 GICOR shows improved biochemical control and OS in high-risk patients if 2 years of adjuvant ADT is combined with high-dose RT [734].
3. EORTC trial 22991 shows that 6 months ADT improves biochemical and clinical DFS irrespective of the dose (70, 74, 78 Gy) in intermediate-risk and low-volume high-risk localised PCa patients [735].
4. A Canadian trial of 600 intermediate-risk patients showed that the addition of ADT to EBRT reduced biochemical failure and PCa deaths, in patients treated with either 70 Gy or 76 Gy [736].

A *post-hoc* meta-analysis of two RCTs has suggested that concomitant/adjuvant ADT may be superior to neoadjuvant ADT, but their heterogeneity means that this observation is hypothesis-generating only [724]. However, a Canadian two-arm dose-escalated (76 Gy) RCT compared neoadjuvant and concomitant with adjuvant short-term ADT in 432 patients with intermediate-risk PCa. After 10 years no significant difference in OS or RT-related grade ≥ 3 GI or GU toxicity was seen [737]. Therefore both regimen in combination with dose escalation are reasonable standards [737].

6.1.3.2 Proton beam therapy

In theory, proton beams are an attractive alternative to photon-beam RT for PCa, as they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak), in contrast to photons which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose.

One RCT on dose escalation (70.2 vs. 79.2 Gy) has incorporated protons for the boost doses of either 19.8 or 28.8 Gy. This trial shows improved outcome with the higher dose but it cannot be used as evidence for the superiority of proton therapy [673]. Thus, unequivocal information showing an advantage of protons over IMRT photon therapy is still not available. Studies from the SEER database and from Harvard describing toxicity and patient-reported outcomes do not point to an inherent superiority of protons [738, 739]. In terms of longer-term GI toxicity, proton therapy might even be inferior to IMRT [739].

A RCT comparing equivalent doses of proton-beam therapy with IMRT is underway. Meanwhile, proton therapy must be regarded as an experimental alternative to photon-beam therapy.

6.1.3.3 Spacer during external beam radiation therapy

Biodegradable spacer insertion involves using a liquid gel or balloon to increase the distance between the prostate and rectum and consequently reduce the amount of radiation reaching the rectum. Various materials have been used with most evidence available for CE-marked hydrogel spacers [740]. A meta-analysis including one RCT and six cohort studies using the hydrogel spacer demonstrated a 5–8% reduction in the rectal volume receiving high-dose radiation, although heterogeneity between studies is found [741]. In the final analysis of the RCT with a median follow-up of 37 months and with approximately two-thirds of patients evaluable, those treated with spacer *in situ* had no deterioration from baseline bowel function whilst those treated without spacer had a lower mean bowel summary score of 5.8 points which met the threshold for a minimally important difference of 4–6 points [742].

This meta-analysis highlights inconsistent reporting of procedural complications. In addition, with more widespread clinical use safety reports describe uncommon, but severe and life changing, complications including prostatic abscess, fistulae and sepsis [743]. Implantation is associated with a learning curve and should only be undertaken by teams with experience of TRUS and transperineal procedures with robust audit reporting in place [744]. Its role in the context of moderate or extreme hypofractionation is as yet unclear.

6.1.3.4 Brachytherapy

6.1.3.4.1 Low-dose rate brachytherapy

Low-dose rate (LDR) brachytherapy uses radioactive seeds permanently implanted into the prostate. There is a consensus on the group of patients with the best outcomes after LDR monotherapy [745] for low- or favourable intermediate-risk and good urinary function defined as an International Prostatic Symptom Score (IPSS) ≤ 12 and maximum flow rate > 15 mL/min on urinary flow tests, as per NCCN definition (see Section 4.2) [746]. In addition, with due attention to dose distribution, patients having had a previous TURP can undergo brachytherapy without an increase in risk of urinary toxicity. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the postero-lateral sides of the prostate and there should be at least a 3-month interval between TURP and brachytherapy to allow for adequate healing [747-750].

The only available RCT comparing RP and LDR brachytherapy as monotherapy was closed due to poor accrual [751]. Outcome data are available from a number of large population cohorts with mature follow-up [752-759]. The biochemical DFS for ISUP grade 1 patients after 5 and 10 years has been reported to range from 71% to 93% and 65% to 85%, respectively [752-759]. A significant correlation has been shown between the implanted dose and biochemical control [760]. A D90 (dose covering 90% of the prostate volume) of > 140 Gy leads to a significantly higher biochemical control rate (PSA < 1.0 ng/mL) after 4 years (92 vs. 68%). There is no OS benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [761].

Low-dose rate brachytherapy can be combined with EBRT in unfavourable intermediate-risk PCa (See Section 4.2) and high-risk patients. External beam RT (total dose of 78 Gy) has been compared with EBRT (total dose 46 Gy) followed by LDR brachytherapy boost (prescribed dose 115 Gy) in intermediate-risk and high-risk patients in the ASCENDE-RT randomised trial with 12 months of ADT in both arms [762]. The LDR boost resulted in 5- and 7-year PSA PFS increase (89% and 86%, respectively, compared to 84% and 75%). This improvement was achieved at a cost of increased late grade 3+ GU toxicity (18% compared to 8%) [763]. Toxicity resulted mainly in the development of urethral strictures and incontinence and great care should be taken during treatment planning.

6.1.3.4.2 High-dose rate brachytherapy

High-dose rate (HDR) brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. The technical differences are outlined in Table 6.1.11. The use of the GEC (Groupe Europeen de Curietherapie)/ESTRO Guidelines is strongly recommended [764]. High-dose rate brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy [765]. A systematic review of non-RCTs and data from population studies suggest outcomes with EBRT plus HDR brachytherapy are superior to EBRT alone [766, 767].

A single centre RCT of EBRT (55 Gy in 20 fractions) vs. EBRT (35.75 Gy in 13 fractions), followed by HDR brachytherapy (17 Gy in two fractions over 24 hours) has been reported [768]. In 218 patients with T1–3 N0M0 PCa the combination of EBRT and HDR brachytherapy showed a significant improvement in the biochemical disease-free rate (p = 0.04) at 5 and 10 years (75% and 46% compared to 61% and 39%). However, an unexpectedly high rate of early recurrences was observed in the EBRT arm alone, even after 2 years, possibly due to a dose lower than the current standard used [768].

Supporting, but not definitive, evidence of the benefit of HDR boost is available from the TROG 03.04 RADAR trial. This multi-centre study had upfront radiation dose escalation (non-randomised) with dosing options of 66, 70, or 74 Gy EBRT, or 46 Gy EBRT plus HDR brachytherapy boost and randomised men with locally-advanced PCa to 6 or 18 months ADT. After a minimum follow-up of 10 years HDR boost significantly reduced distant progression, the study primary endpoint (sub HR: 0.68, 95% CI: 0.57–0.80; p < 0.0001), when compared to EBRT alone and, independent of duration of ADT, HDR boost was associated with increased IPSS of 3 points at 18 months post-treatment resolving by 3 years but decreased rectal symptoms when compared to EBRT [769].

Although radiation dose escalation using brachytherapy boost provides much higher biological doses, the TROG 03.04 RADAR RCT and systematic reviews show ADT use independently predicts better outcomes regardless of radiation dose intensification [761, 769, 770]. Omitting ADT may result in inferior OS and based on current evidence ADT use and duration should be in line with that used when delivering EBRT alone.

Fractionated HDR brachytherapy as monotherapy can be offered to patients with low- and intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres. Five-year PSA control rates of 97.5% and 93.5% for low- and intermediate-risk PCa, respectively, are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [771]. Single fraction HDR monotherapy should not be used as it has inferior biochemical control rates compared to fractionated HDR monotherapy [772].

Table 6.1.11: Difference between LDR and HDR brachytherapy

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	• Permanent seeds implanted • Uses Iodine-125 (I-125) (most common), Palladium-103 (Pd-103) or Cesium-131 isotopes • Radiation dose delivered over weeks and months • Acute side effects resolve over months • Radiation protection issues for patient and carers
High dose rate (HDR)	• Temporary implantation • Iridium-192 (IR-192) isotope introduced through implanted needles or catheters • Radiation dose delivered in minutes • Acute side effects resolve over weeks • No radiation protection issues for patient or carers

6.1.3.5 Acute side effects of external beam radiotherapy and brachytherapy

Gastro-intestinal and urinary side effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of grade 1, 20% of grade 2, and 2% grade 3. In the same trial, approximately 30% of patients reported acute grade 1 GI toxicity, 10% grade 2, and less than 1% grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [686]. In addition, general side effects such as fatigue are common. It should be noted that the incidence of acute side effects is greater than that of late effects (see Section 8.2.2.1), implying that most acute effects resolve. In a RCT of conventional dose EBRT vs. EBRT and LDR brachytherapy the incidence of acute proctitis was reduced in the brachytherapy arm, but other acute toxicities were equivalent [762]. Acute toxicity of HDR brachytherapy has not been documented in a RCT, but retrospective reports confirm lower rates of GI toxicity compared with EBRT alone and grade 3 GU toxicity in 10%, or fewer, patients, but a higher incidence of urinary retention [773]. Similar findings are reported using HFX; in a pooled analysis of 864 patients treated using extreme HFX and stereotactic RT, declines in urinary and bowel domains were noted at 3 months which returned to baseline, or better, by 6 months [774].

6.1.4 ***Hormonal therapy***

6.1.4.1 Introduction

6.1.4.1.1 Different types of hormonal therapy

Androgen deprivation can be achieved by suppressing the secretion of testicular androgens in different ways. This can be combined with inhibiting the action of circulating androgens at the level of their receptor which has been known as complete (or maximal or total) androgen blockade (CAB) using the old-fashioned anti-androgens [775].

6.1.4.1.1.1 Testosterone-lowering therapy (castration)

6.1.4.1.1.1.1 Castration level

The castration level of testosterone is < 50 ng/dL (1.7 nmol/L), which was defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15 ng/dL [776]. Therefore, a more appropriate level should be defined as < 20 ng/dL (1 nmol/L). This definition is important as better results are repeatedly observed with lower testosterone levels compared to 50 ng/dL [777-779]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still the historical < 50 ng/dL (1.7 nmol/L).

6.1.4.1.1.1.2 Bilateral orchiectomy

Bilateral orchiectomy or subcapsular pulpectomy is still considered the primary treatment modality for ADT. It is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia, and it is the quickest way to achieve a castration level which is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment [780].

6.1.4.1.1.1.3 Oestrogens

Treatment with oestrogens results in testosterone suppression and is not associated with bone loss [781]. Early studies tested oral diethylstilboestrol (DES) at several doses. Due to severe side effects, especially thromboembolic complications, even at lower doses these drugs are not considered as standard first-line treatment [782-784].

6.1.4.1.1.1.4 Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly, basis. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosterone surge' or 'flare-up' phenomenon which starts two to three days after administration and lasts for about one week. This may lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [785]. Patients at risk are usually those with high-volume symptomatic bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare but does not completely remove the risk. Anti-androgen therapy is usually continued for 4 weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. In addition, the long-term impact of preventing 'flare up' is unknown [786, 787].

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within 2 to 4 weeks [788]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [789]. So far, no survival difference between LHRH agonists and orchiectomy has been reported due to the lack of high-quality trials [790].

The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.1.4.1.1.1.5 Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone-releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with, so far, only monthly formulations being available. Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [788]. A phase III RCT compared degarelix to monthly leuprorelin following up patients for 12 months, suggesting a better PSA PFS for degarelix 240/80 mg compared to monthly leuprorelin [791]. A systematic review did not show a major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond 12 months as well as the lack of survival data [792]. Its definitive superiority over the LHRH analogues remains to be proven. Short-term follow-up data from a meta-analysis indicate that the use of GnRH antagonist is associated with significantly lower overall mortality and cardiovascular events as compared with agonists. On the other hand, other adverse effects such as decreased libido, hot flushes, ED, weight gain, and injection site reactions are seen less often with the agonists [793, 794].

Relugolix is an oral gonadotropin-releasing hormone antagonist. It was compared to the LHRH agonist leuprolid in a randomised phase III trial [795]. The primary endpoint was sustained testosterone suppression to castrate levels through 48 weeks. There was a significant difference of 7.9 percentage points (95% CI: 4.1–11.8) showing non-inferiority and superiority of relugolix. The incidence of major adverse cardiovascular events was significantly lower with relugolix (prespecified safety analysis). Relugolix has been approved by the FDA [796].

6.1.4.1.1.1.6 Anti-androgens

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g., cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
- non-steroidal or pure, e.g., nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal anti-androgens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

6.1.4.1.1.1.6.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side effects are secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side effects are cardiovascular toxicity (4–40% for CPA) and hepatotoxicity.

Cyproterone acetate was the first licensed anti-androgen but the least studied. Its most effective dose as monotherapy is still unknown. Although CPA has a relatively long half-life (31–41 hours), it is usually administered in two or three fractionated doses of 100 mg each. In one RCT CPA showed a poorer OS when compared with LHRH analogues [797]. An underpowered RCT comparing CPA monotherapy with flutamide

in M1b PCa did not show any difference in DSS and OS at a median follow-up of 8.6 years [798]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

6.1.4.1.1.1.6.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy with e.g., nilutamide, flutamide or bicalutamide does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [799]. Non-androgen-related pharmacological side effects differ between agents. Bicalutamide shows a more favourable safety and tolerability profile than flutamide and nilutamide [800]. The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side effects are mainly gynaecomastia (70%) and breast pain (68%). However, non-steroidal anti-androgen monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [799, 801]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.1.4.1.1.2 New androgen pathway targeting agents (ARTA)

Once on ADT the development of castration-resistance (CRPC) is only a matter of time. It is considered to be mediated through two main overlapping mechanisms: androgen-receptor (AR)-independent and AR-dependent mechanisms (see Section 6.5 - Castrate-resistant PCa). In CRPC, the intracellular androgen level is increased compared to androgen sensitive cells and an over-expression of the AR has been observed, suggesting an adaptive mechanism [802]. This has led to the development of several new compounds targeting the androgen axis. In mCRPC, AAP and enzalutamide have been approved. In addition to ADT (sustained castration), AAP, apalutamide and enzalutamide have been approved for the treatment of metastatic hormone sensitive PCa (mHSPC) by the FDA and the EMA. For the updated approval status see EMA and FDA websites [803-807]. Finally, apalutamide, darolutamide and enzalutamide have been approved for non-metastatic CRPC (nmCRPC) at high risk of further metastases [808-812].

6.1.4.1.1.2.1 Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-hydrolase and 17,20-lyase inhibition). By blocking CYP17, abiraterone acetate significantly decreases the intracellular testosterone level by suppressing its synthesis at the adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone to prevent drug-induced hyperaldosteronism [803, 806].

6.1.4.1.1.2.2 Apalutamide, darolutamide, enzalutamide (alphabetical order)

These agents are novel non-steroidal anti-androgens with a higher affinity for the AR receptor than bicalutamide. While previous non-steroidal anti-androgens still allow transfer of ARs to the nucleus and would act as partial agonists, all three agents also block AR transfer and therefore suppress any possible agonist-like activity [807-809]. Darolutamide has structurally unique properties [808]. In particular, in preclinical studies, it showed not to cross the blood-brain barrier [813, 814].

6.1.4.1.1.3 New compounds

6.1.4.1.1.3.1 PARP inhibitors

Poly (ADP-ribose) polymerase inhibitors (PARPi) block the enzyme poly ADP ribose polymerase (PARP) and were developed aiming to selectively target cancer cells harbouring *BRCA* mutations and other mutations inducing homologous recombination deficiency and high level of replication pressure with a sensitivity to PARPi treatment. Due to the oncogenic loss of some DNA repair effectors and incomplete DNA repair repertoire, some cancer cells are addicted to certain DNA repair pathways such as Poly (ADP-ribose) polymerase (PARP)-related single-strand break repair pathway. The interaction between *BRCA* and PARP is a form of synthetic lethal effect which means the simultaneously functional loss of two genes lead to cell death, while a defect in any single gene only has a limited effect on cell viability [815]. The therapeutic indication for PCa is discussed in Section 6.5.8.1.

6.1.4.1.1.3.2 Immune checkpoint inhibitors

Immune checkpoints are key regulators of the immune system. Checkpoint proteins, such as B7-1/B7-2 on antigen-presenting cells (APC) and CTLA-4 on T cells, help keep the immune responses in an equilibrium. The binding of B7-1/B7-2 to CTLA-4 keeps the T cells in the inactive state whilst an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and to kill tumour cells.

Approved checkpoint inhibitors target the molecules CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). Programmed death-ligand 1 is the transmembrane programmed cell death 1 protein which interacts with PD-L1 (PD-1 ligand 1). Cancer-mediated upregulation of PD-L1 on the cell surface may inhibit T cells. Antibodies that bind to either PD-1 or PD-L1 and therefore block the interaction may allow the T cells to induce cell killing. Examples of PD-1 inhibitors are pembrolizumab and nivolumab; of

PD-L1 inhibitors, atezolizumab, avelumab and durvalumab and an example of CTLA4 inhibitors is ipilimumab [816, 817]. Therapeutic use is discussed in Section 6.5.10.

6.1.4.1.1.3.3 Protein kinase B (AKT) inhibitors

Aberrant activation of the PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase)/AKT pathway, predominately due to PTEN loss (phosphatase and tensin homologue deleted from chromosome 10), is common in PCa (40–60% of mCRPC) and is associated with worse prognosis. The androgen receptor signalling and AKT pathway are reciprocally cross-regulated, so that inhibition of one leads to upregulation of the other. AKT inhibitors are small molecules which are designed to target and bind to all three isoforms of AKT, which is a key component of the PI3K/AKT pathway and a key driver of cancer cell growth. Ipatasertib is an oral, highly specific, AKT inhibitor which shows clinically significant activity when combined with abiraterone acetate in patients with loss of the tumour suppressor protein PTEN (on IHC) within the tumour [818, 819]. The therapeutic indication for PCa is discussed in Section 6.5.6.5.

6.1.4.1.1.3.4 Radiopharmaceutical therapy

Radiopharmaceutical therapy (RPT) is based on the delivery of radioactive atoms to tumour-associated targets. The mechanism of action for RPT is radiation-induced killing of cells. Radionuclides with different emission properties are used to deliver radiation. The most commonly used radionuclides are represented by β-particles (e.g., ^{177}Lu) or α-particles (e.g. ^{223}Ra, ^{225}Ac). ^{177}Lu is increasingly used because of its optimal imaging range (100–200 keV), favourable half time (6.6 days) and appropriate β-particle energy for therapy.

The short path of the β-particles (0.05–0.08 mm) results in minimal toxic effects in adjacent healthy tissue. These properties enable such radionuclides to be used as theranostics (i.e., the same radionuclide may be used for both diagnostic and therapeutic purposes). However, an essential requirement prior to any RPT is to assess the targeting of the agent, mainly using PET techniques which show the tumour expression and the extent of cancer [820].

*6.1.5 **Investigational therapies***

6.1.5.1 Background

Besides RP, EBRT and brachytherapy, other modalities have emerged as potential therapeutic options in patients with clinically localised PCa [821-824]. In this section, both whole gland- and focal treatment will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy) and focal photodynamic therapy, as sufficient data are available to form the basis of some initial judgements. Other options such as radiofrequency ablation (RFA) and electroporation, among others, are considered to be in the early phases of evaluation [825]. In addition, a relatively newer development is focal ablative therapy [825, 826] whereby lesion-targeted ablation is undertaken in a precise organ-sparing manner. All these modalities have been developed as minimally-invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity, and improved functional outcomes.

6.1.5.2 Cryotherapy

Cryotherapy uses freezing techniques to induce cell death by dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals and vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [821-824]. Freezing of the prostate is ensured by the placement of 17 gauge cryo-needles under TRUS guidance, placement of thermosensors at the level of the external sphincter and rectal wall, and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryotherapy devices are mainly used. Since its inception, cryotherapy has been used for whole-gland treatment in PCa either as a primary or salvage treatment option.

The main adverse effects of cryosurgery are ED (18%), urinary incontinence (2–20%), urethral sloughing (0–38%), rectal pain and bleeding (3%) and recto-urethral fistula formation (0–6%) [827]. There is a lack of prospective comparative data regarding oncological outcomes of whole-gland cryosurgery as a curative treatment option for men with localised PCa, with most studies being non-comparative single-arm case series with short follow-up [827].

6.1.5.3 High-intensity focused ultrasound

High-intensity focused US consists of focused US waves emitted from a transducer that cause tissue damage by mechanical and thermal effects as well as by cavitation [828]. The goal of HIFU is to heat malignant tissue above 65°C so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anaesthesia, with the patient lying in the lateral or supine position. High-intensity focused US has previously been widely used for whole-gland therapy. The major adverse effects of HIFU include acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), recto-urethral fistula

(0–5%) and urinary incontinence (10%) [827]. Disadvantages of HIFU include difficulty in achieving complete ablation of the prostate, especially in glands larger than 40 mL, and in targeting cancers in the anterior zone of the prostate. Similar to cryosurgery, the lack of any long-term prospective comparative data on oncological outcomes prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [827].

6.1.5.4 Focal therapy

During the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness leading to the adoption of both formal and informal screening strategies. The effect of this has been that men are identified at an earlier stage with smaller tumours that occupy only 5–10% of the prostate volume, with a greater propensity for unifocal or unilateral disease [829-831]. Most focal therapies to date have been achieved with ablative technologies: cryotherapy, HIFU, photodynamic therapy, electroporation, and focal RT by brachytherapy or CyberKnife® Robotic Radiosurgery System technology (Accuray Inc., Sunnyvale, CA, USA). The main purpose of focal therapy is to ablate tumours selectively whilst limiting toxicity by sparing the neurovascular bundles, sphincter and urethra [832-834].

A systematic review and network meta-analysis on ablative therapy in men with localised PCa performed a sub-group analysis of focal therapy vs. RP and EBRT [827]. Nine case series reporting on focal therapy were identified (5 studies reporting on focal cryosurgical ablation of the prostate [CSAP], three studies on focal HIFU, and one study reported on both). For focal CSAP vs. RP or EBRT, no statistically significant differences were found for BCR at 3 years. For focal HIFU vs. RP or EBRT there were neither comparable data on oncological-, continence- nor potency outcomes at one year or more. More recently, Valerio *et al.*, performed a systematic review to summarise the evidence regarding the effectiveness of focal therapy in localised PCa [826]. Data from 3,230 patients across 37 studies were included, covering different energy sources including HIFU, CSAP, photodynamic therapy, laser interstitial thermotherapy, focal brachytherapy, irreversible electroporation and radiofrequency ablation. The overall quality of the evidence was low, due to the majority of studies being single-centre, non-comparative and retrospective in design, heterogeneity of definitions and approaches, follow-up strategies, outcomes, and duration of follow-up. Although the review suggests that focal therapy has a favourable toxicity profile in the short-to-medium term, its oncological effectiveness remains unproven due to lack of reliable comparative data against standard interventions such as RP and EBRT.

In order to update the evidence base, a systematic review incorporating a narrative synthesis was performed by the Panel, including comparative studies assessing focal ablative therapy vs. radical treatment, AS or alternative focal ablative therapy, published between 1st January 2000 and 12th June 2020 [835]. In brief, out of 1,119 articles identified, 4 primary studies (1 RCT and 3 retrospective cohort studies) [836-840] recruiting 3,961 patients, and 10 systematic reviews were included [827]. Only qualitative synthesis was possible due to clinical heterogeneity. Overall risk of bias (RoB) and confounding were moderate to high. Comparative effectiveness data regarding focal therapy were inconclusive. Data quality and applicability were poor due to clinical heterogeneity, RoB and confounding, lack of long-term data, inappropriate outcome measures and poor external validity. The majority of systematic reviews had a low or critically low confidence rating.

The only identified RCT, Azzouzi *et al.*, deserves discussion [836]. The authors compared focal therapy using padeliporfin-based vascular-targeted photodynamic therapy (PDT) vs. AS in men with very low-risk PCa. The study found, at a median follow-up of 24 months, that less patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24–0.46), and needed less radical therapy (6% vs. 29%, $p < 0.0001$). In addition, more men in the PDT arm had a negative prostate biopsy at two years than men in the AS arm (adjusted RR: 3.67, 95% CI: 2.53–5.33). Updated results were published in 2018 showing that these benefits were maintained after four years [837]. Nevertheless, limitations of the study include inappropriately comparing an intervention designed to destroy cancer tissue in men with low-risk PCa against an intervention primarily aimed at avoiding unnecessary treatment in men with low-risk PCa, and an unusually high observed rate of disease progression in the AS arm (58% in two years). Furthermore, more patients in the AS arm chose to undergo radical therapy without a clinical indication which may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy or any MRI scanning, which is not representative of contemporary practice. Given the lack of robust comparative data on medium- to long-term oncological outcomes for focal therapy against curative interventions (i.e. RP or EBRT), significant uncertainties remain in regard to focal therapy as a proven alternative to either AS or radical therapy. Consequently, robust prospective trials reporting standardised outcomes [841] are needed before unrestricted recommendations in support of focal therapy for routine clinical practice can be made [825, 841, 842]. For now, the available evidence indicates that focal therapy should be performed within the context of a clinical trial setting or well-designed prospective cohort study. It is hoped that more mature and robust data demonstrating long-term efficacy in the next few years will provide the necessary evidence which will facilitate its wider implementation and acceptance.

6.1.6 *General guidelines for the treatment of prostate cancer*

Recommendations	Strength rating
Inform patients that based on robust current data with up to 12 years of follow-up, no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all active local treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.	Strong
Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined into a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or intermediate-risk disease with ISUP grade 2 and ≤ 33% of biopsy cores involved.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10–20 ng/mL.	Weak
Offer LDR or HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Offer whole-gland cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

6.2 Treatment by disease stages

6.2.1 *Treatment of low-risk disease*

6.2.1.1 *Active surveillance*

The main risk for men with low-risk disease is over treatment (see Sections 6.1.1.2 and 6.1.1.4); therefore, AS should be considered for all such patients.

6.2.1.1.1 Active surveillance - inclusion criteria

Guidance regarding selection criteria for AS is limited by the lack of data from prospective RCTs. As a consequence, the Panel undertook an international collaborative study involving healthcare practitioners and patients to develop consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS (DETECTIVE Study) [284], as well as a formal systematic review on the various AS protocols [843]. The criteria most often published include: ISUP grade 1, clinical stage cT1c or cT2a, PSA < 10 ng/mL and PSA-D < 0.15 ng/mL/cc [517, 844]. The latter threshold remains controversial [844, 845]. These criteria were supported by the DETECTIVE consensus. There was no agreement on the maximum number of cores that can be involved with cancer or the maximum percentage core involvement (CI), although there was recognition that extensive disease on MRI should exclude men from AS [284]. A systematic review and meta-analysis found three clinico-pathological variables which were significantly associated with reclassification, which included PSA-D, > 2 positive cores, and African-American race [846]. In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were

present: predominant ductal carcinoma (including pure intraductal carcinoma), cribriform histology, sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [382] and perineural invasion [847].

Recently, a multidisciplinary consensus conference on germline testing attempted to develop a genetic implementation framework for the management of PCa [165]. Based on consensus, *BRCA2*-gene testing was recommended for AS discussions. However, the nature of such discussions and how a positive result influences management were beyond the scope of the project. Currently, if included in AS programmes, patients with a *BRCA2* mutation should be cautiously monitored until such time that more robust data are available.

6.2.1.1.2 Tissue-based prognostic biomarker testing

Biomarkers, including Oncotype Dx®, Prolaris®, Decipher®, PORTOS and ProMark® are promising (see Section 5.2.8.3). However, further data will be needed before such markers can be used in standard clinical practice [236].

6.2.1.1.3 Magnetic resonance imaging for selection for active surveillance

In men eligible for AS based upon systematic biopsy findings alone who did not have a pre-biopsy MRI, a re-biopsy within 6–12 months (usually referred to as 'confirmatory biopsy') seems mandatory to exclude sampling error [844, 848]. Magnetic resonance imaging can also improve the detection of aggressive cancers [849, 850]. A systematic review showed that men with positive baseline MRI have an, approximately, 3-fold higher chance (RR: 2.77, 95% CI: 1.76–4.38) of upgrading to an ISUP grade ≥ 2 cancer than men with negative MRI [851]. More recent studies of patients on AS for ISUP 1 cancer confirmed that a positive baseline MRI was a significant predictor of upgrading to ISUP grade ≥ 2 cancer and of unfavourable disease at RP [852, 853]. This is also true when upgrading is defined as progression to ISUP grade ≥ 3 cancer [854, 855]. Of note, MRI keeps its significant predictive power for upgrading when other strong predictors such as age or PSA-D are accounted for [853, 855, 856].

At confirmatory biopsy, adding MRI-targeted biopsy to systematic biopsy improves upgrade detection rates by increments of 3.3 to 7.9 per 100 men depending on the series [857]. However, systematic biopsy retains substantial added value [851].

A meta-analysis evaluated the proportion of men eligible for AS based on systematic TRUS-guided biopsy in whom the cancer was upgraded by MRI-targeted biopsy (17%) and systematic biopsy (20%) at confirmatory biopsy [851]. Ten percent of patients were upgraded by both biopsy methods, meaning MRI-targeted biopsy upgraded an additional 7% (95% CI: 5–10%) of men, whilst systematic biopsy upgraded an additional 10% of men (95% CI: 8–14%). Even if the analysed series used different definitions for cancer upgrading, combining the two biopsy techniques appears to be the best way to select patients for AS at confirmatory biopsy.

The Active Surveillance Magnetic Resonance Imaging Study (ASIST) randomised men on AS scheduled for confirmatory biopsy to either 12-core systematic biopsy or to MRI with targeted biopsy (when indicated) combined with systematic biopsy (up to 12 cores in total). After 2 years of follow-up, use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%, p = 0.017) and in fewer patients progressing to ISUP grade ≥ 2 cancer (9.9% vs. 23%, p = 0.048) [858].

At the DETECTIVE consensus meeting it was agreed that men eligible for AS after combined systematic- and MRI-targeted biopsy do not require a confirmatory biopsy [284].

6.2.1.1.4 Follow-up during active surveillance

Based on the DETECTIVE consensus study, the follow-up strategy should be based on serial DRE (at least once yearly), PSA (at least once, every 6 months) and repeated biopsy. It was also agreed that PSA progression or change in PSA kinetics alone should lead to reclassification only if accompanied by changes in histology on repeat biopsy [284].

In 2016, the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria were established to standardise the assessment of tumour progression on serial MRI [859]. Progression on MRI, defined using the PRECISE criteria, or not, is a strong predictor of histological upgrading [860]. Two independent meta-analyses assessed the value of MRI progression criteria for predicting histological progression (mostly defined as progression to ISUP grade ≥ 2). The pooled histological progression rate was 27% in both reviews. If biopsies were triggered only by MRI progression findings, approximately two thirds of the biopsies would be avoided, at the cost of missing 40% of men with histological progression. In addition, at least half of biopsied men would have had negative findings for histological progression and thus would have undergone unnecessary biopsies. If histological progression was restricted to progression to ISUP grade ≥ 3, approximately 30% of histological progression would be missed and approximately 80% of the biopsies performed would be unnecessary. The use of the PRECISE criteria did not seem to change these results [861, 862].

Combining MRI finding with PSA-D [855, 863, 864] or PSA kinetics [850, 865] may improve the prediction of histological progression, prompting, for example, the biopsy of all patients with elevated PSA-D

regardless of MRI findings, or avoiding biopsy only when MRI does not show progression and the PSA level is stable. Combining MRI with other biomarkers may also help selecting patients for follow-up biopsy [866, 867]. Nonetheless, the level of evidence of these studies remains low and therefore, protocol-mandated, untriggered follow-up biopsies seem necessary [284].

A Panel systematic review incorporating 263 surveillance protocols showed that 78.7% of protocols mandated per-protocol confirmatory biopsies within the first 2 years and that 57.7% of the protocols performed repeat-biopsy at least every 3 years for 10 years after the start of AS [843]. In a single centre AS cohort of 514 patients who underwent at least three protocol-mandated biopsies after diagnosis (the confirmatory biopsy and at least two additional surveillance biopsies), men with one negative biopsy (i.e., no cancer at all) at confirmatory or second biopsy, or men with two consecutive negative biopsies had a lower likelihood of positive third biopsy and significantly better 10-year treatment-free survival [868]. This suggests that men with repetitive negative biopsies may pursue AS with at least less frequent untriggered biopsies.

6.2.1.1.5 Active Surveillance - change in treatment

Men may remain on AS whilst they continue to consent, have a life expectancy of > 10 years and the disease remains indolent. Patient anxiety about continued surveillance occurs in around 10% of patients on AS [869] and was recognised as a valid reason for active treatment [284]. More common is the development of other co-morbidities which may result in a decision to transfer to a WW strategy.

A PSA change alone (including PSA-DT < 3 years) should not change management based on its weak link with grade progression [870, 871] but rather trigger further investigation. There was clear agreement in the DETECTIVE consensus meeting that a change in PSA should lead to repeat-MRI and repeat-biopsy. It was also agreed that changes on follow-up MRI needed a confirmatory biopsy before considering active treatment [284].

However, the histopathology criteria required to trigger a change in management in the targeted biopsy era remain debated. Magnetic resonance imaging-targeted biopsy induces a grade shift and ISUP 2-3 cancers detected by MRI-targeted biopsy have, on average, better prognosis than those detected by systematic sampling (see Section 5.2.4.2.6.4). As an increasing number of men with favourable intermediate-risk disease are managed with AS, it seems illogical to use progression to ISUP grade 2 based on targeted biopsies as the sole criterion for reclassification. In addition, as acknowledged in the DETECTIVE consensus meeting, the number of positive cores is not an indicator of tumour volume anymore if targeted biopsies are performed [284, 866]. No agreement could be reached on the pathological criteria required to trigger a change in management during the DETECTIVE consensus meeting [284]. However, based on the findings of a systematic review incorporating 271 reclassification protocols, patients with low-volume ISUP 2 disease at recruitment, and with increased core positivity (> 3 cores) and/or core involvement (> 50% per core) on repeat systematic biopsies not using MRI, should be reclassified [843].

6.2.1.2 Alternatives to active surveillance

In terms of alternatives to AS in the management of patients with low-risk disease there is some data from randomised studies. In the PIVOT trial (Section 6.1.1.3.1) which compared surgery vs. observation, only 42% of patients had low-risk disease [527]. Sub-group analysis revealed that for low-risk disease there was no statistically significant difference in all-cause mortality between surgery vs. observation (RR: 0.93, 95% CI: 0.78–1.11). In the ProtecT study (Section 6.1.1.4) which compared AM vs. surgery vs. EBRT, 56% of patients had low-risk disease [516]. However, no sub-group analysis on disease risk was performed on this population. The study found no difference between the three arms in terms of OS and CSS, but AM had higher metastatic progression compared with surgery or EBRT (6.0% vs. 2.6%). There are no robust data comparing contemporary AS protocols with either surgery or EBRT in patients with low-risk disease. On balance, although AS should be the default management strategy in patients with low-risk disease and a life expectancy > 10 years, it would be reasonable to consider surgery and EBRT as alternatives to AS in patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.

6.2.1.2.1 ADT monotherapy

Data regarding the use of ADT monotherapy in men with low-risk localised disease may be inferred indirectly from the Early Prostate Cancer (EPC) Trial Programme which published its findings in 2006 [872]. The EPC programme comprises three large RCTs including 8,113 men with localised (cT1–2, N0/NxM0) or locally advanced (cT3–4, any N; or any T, N+, M0) PCa. The intervention was oral bicalutamide 150 mg monotherapy vs. placebo following standard care (defined as RP, radical EBRT or WW). The primary endpoints were PFS and OS. Patients were stratified according to clinical stage only; data regarding PSA and Gleason score were not assessed. The authors found in patients with localised disease, ADT monotherapy did not improve PFS nor OS in any of the subgroups, compared with placebo. Instead, there was a statistically insignificant numerical

trend towards worse OS with ADT in the WW sub-group (HR: 1.16, 95% CI: 0.99–1.37; p = 0.07). Although the trial did not directly address men with low-risk disease, it offered some evidence suggesting that otherwise asymptomatic men with localised disease should not receive ADT monotherapy. Currently, there is no evidence supporting the use of ADT monotherapy in asymptomatic men with low-risk disease who are not eligible for any local/radical treatment; these men should simply be offered WW alone.

Other treatments such as whole-gland ablative therapy (f.i. cryotherapy or HIFU) or focal ablative therapy remain unproven in the setting of localised low-risk disease compared with AS or radical treatment options; these have been discussed in detail in Section 6.1.5.

6.2.1.3 Summary of evidence and guidelines for the treatment of low-risk disease

Summary of evidence	**LE**
Systematic biopsies have been scheduled in AS protocols, the number and frequency of biopsies varied, there is no approved standard.	NR

Recommendations	**Strength rating**
Active surveillance (AS)	
Selection of patients	
Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
Patients with intraductal and cribiform histology on biopsy should be excluded from AS.	Strong
Perform magnetic resonance imaging (MRI) before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Follow-up of patients	
Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
In case of prostate-specific antigen progression or change in digital-rectal examination or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
Active treatment	
Offer surgery or radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	
Do not perform a PLND.	Strong
Radiotherapeutic treatment	
Offer low-dose rate brachytherapy to patients with low-risk PCa and good urinary function.	Strong
Use intensity-modulated radiation therapy/volumetric modulated arc therapy plus image-guided radiation therapy with a total dose of 74–80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
Other therapeutic options	
Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Strong
Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong

*6.2.2 **Treatment of intermediate-risk disease***

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13.0% and 19.6%, respectively [873]. These estimates are based on systematic biopsies and may be overestimated in the era of MRI-targeted biopsies.

6.2.2.1 Active Surveillance

In the ProtecT trial, up to 22% of the randomised patients in the AM arm had ISUP grade > 1 and 10% a PSA > 10 ng/mL [516]. A Canadian consensus group proposes that low volume ISUP grade 2 (< 10% Gleason pattern 4 on systematic biopsies) may also be considered for AS. These recommendations have been endorsed by the American Society of Clinical Oncology (ASCO) [874] and the recent DETECTIVE consensus

meeting [284] for those patients with a PSA < 10 ng/mL and low core positivity. The DETECTIVE Study concluded that men with favourable ISUP 2 cancer (PSA < 10 ng/mL, clinical stage ≤ cT2a and a low number of positive systematic cores) should also be considered for deferred treatment [284]. In this setting, re-biopsy within 6 to 12 months to exclude sampling error is mandatory [844, 848] even if this could be modified in the future [875]. The DETECTIVE consensus group were clear that those with ISUP 3 disease should not be considered for AS. It is clear that the presence of any grade 4 pattern is associated with a 3-fold increased risk of metastases compared to ISUP grade 1, while a PSA up to 20 ng/mL might be an acceptable threshold [848, 876, 877], especially in the context of low PSA-D. In addition, it is likely that MRI and targeted biopsies will detect small foci of Gleason 4 cancer that might have been missed with systematic biopsy. Therefore, care must be taken when explaining this treatment strategy especially to patients with the longest life expectancy.

Enikeev *et al.*, performed a systematic review and meta-analysis to assess the outcomes of AS in patients with intermediate-risk PCa to summarise available data on its oncological outcomes in comparison with low-risk disease [878]. The definition of AS was not provided by the authors; instead the search strategy included 'active surveillance' as a search term, and no *a priori* study protocol was available. The primary outcome was the proportion of patients who remained on AS, whilst secondary outcomes included CSS, OS, and metastasis-free survival. Seventeen studies were included, incorporating 6,591 patients with intermediate-risk disease. Sixteen studies included patients with low- and intermediate-risk disease, hence enabling comparative outcome assessment via pooled analysis. Only one study performed MRI at recruitment and follow-up. There was significant clinical heterogeneity in terms of inclusion criteria for intermediate-risk disease. The results showed the proportion of patients who remained on AS was comparable between the low- and intermediate-risk groups after 10 and 15 years' follow-up (OR: 0.97, 95% CI: 0.83–1.14; and OR: 0.86, 95% CI: 0.65–1.13). Cancer-specific survival was worse in the intermediate-risk group after 10 years (OR: 0.47, 95% CI: 0.31–0.69) and 15 years (OR: 0.34, 95% CI: 0.2–0.58). Overall survival was not statistically significantly different at 5 years' follow-up (OR: 0.84, 95% CI: 0.45–1.57) but was significantly worse in the intermediate-risk group after 10 years (OR: 0.43, 95% CI: 0.35–0.53). Metastases-free survival did not significantly differ after 5 years (OR: 0.55, 95% CI: 0.2–1.53) but was worse in the intermediate-risk group after 10 years (OR: 0.46, 95% CI: 0.28–0.77). The authors concluded that AS could be offered to patients with intermediate-risk disease but they should be informed of a higher rate of progression.

The DETECTIVE Study-related qualitative systematic review aimed to determine appropriate criteria for inclusion of intermediate-risk disease into AS protocols [843]. Out of 371 AS protocols included in the review, more than 50% included patients with intermediate-risk disease on the basis of PSA up to 20 ng/mL (25.3%), ISUP 2 or 3 (27.7%), clinical stage cT2b/c (41.6%) and/or direct use of D'Amico risk grouping of intermediate-risk or above (51.1%).

Consequently, AS can be cautiously considered in patients with low-volume ISUP 2 (defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement CI/per core) or another single element of intermediate-risk disease (i.e. favourable intermediate-risk disease) except ISUP 3 disease, which should be excluded. The monitoring schedule should also be more intensive, given the significantly higher risk of progression, development of regional or distant metastases and death of this group compared with low-risk disease. During monitoring, if repeat non-MRI-based systematic biopsies reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease, patients should be reclassified (i.e. actively treated).

6.2.2.2 Radical prostatectomy

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RRP vs. WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71, 95% CI: 0.53–0.95), death from PCa (RR: 0.38, 95% CI: 0.23–0.62) and distant metastases (RR: 0.49, 95% CI: 0.32–0.74) were significantly reduced in intermediate-risk PCa at 18 years. In the PIVOT trial, according to a pre-planned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69, 95% CI: 0.49–0.98), but not death from PCa (0.50, 95% CI: 0.21–1.21) at 10 years. A meta-analysis based on the findings of SPCG-4, PIVOT and ProtecT demonstrated a benefit from RP over observation with a significantly decreased risk of death of 9% and of disease progression of 43% [879]. However, no stratification by disease stages was performed. The risk of having positive LNs in intermediate-risk PCa is between 3.7–20.1% [880]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% [426] or 7% if using the nomogram by Gandaglia *et al*., which incorporates MRI-guided biopsies [429]. In all other cases eLND can be omitted, which means accepting a low risk of missing positive nodes. Nerve sparing surgery is discussed in Section 6.1.2.3.6.

6.2.2.3 Radiation therapy

6.2.2.3.1 Recommended IMRT/VMAT for intermediate-risk PCa

Patients suitable for ADT can be given combined IMRT/VMAT with short-term ADT (4–6 months) [881-883]. For patients unsuitable (e.g., due to co-morbidities) or unwilling to accept ADT (e.g. to preserve their sexual health)

the recommended treatment is IMRT/VMAT (76–78 Gy) or a combination of IMRT/VMAT and brachytherapy as described below (see Section 6.2.3.2.3).

6.2.2.3.2 Brachytherapy for intermediate-risk PCa

The authors of a systematic review of LDR brachytherapy recommend that LDR brachytherapy monotherapy can be offered to patients with NCCN favourable intermediate-risk disease and good urinary function (see Section 4.2) [884]. Fractionated HDR brachytherapy as monotherapy can be offered to selected patients with intermediate-risk PCa although they should be informed that results are only available from small series in very experienced centres. Five-year PSA control rates over 90% are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [771]. There are no direct data to inform on the use of ADT in this setting. Trimodality therapy with IMRT plus brachytherapy boost and short-term ADT can be considered for NCCN unfavourable intermediate-risk PCa (see Section 4.2) but patients should be made aware that the potential improvements in biochemical control are accompanied with an increased risk of long-term urinary problems [762, 763, 767].

6.2.2.4 Other options for the primary treatment of intermediate-risk PCa (experimental therapies)

6.2.2.4.1 Focal therapy

A prospective study on focal therapy using HIFU in patients with localised intermediate-risk disease was published but the data was derived from an uncontrolled single-arm case series [842]. There is a paucity of high-certainty data for either whole-gland or focal ablative therapy in the setting of intermediate-risk disease. Consequently, neither whole-gland treatment nor focal treatment can be considered as standard therapy for intermediate-risk patients and, if offered, it should only be in the setting of clinical trials [825].

6.2.2.4.2 Androgen deprivation therapy monotherapy

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from the EORTC 30891 trial, which was a RCT comparing deferred ADT vs. immediate ADT in 985 patients with T0–4 N0–2 M0 disease [880]. The trial showed a small, but statistically significant, difference in OS in favour of immediate ADT monotherapy but there was no significant difference in CSS, predominantly because the risk of cancer-specific mortality was low in patients with PSA < 8 ng/mL. Consequently, the use of ADT monotherapy for this group of patients is not considered as standard, even if they are not eligible for radical treatment.

6.2.2.5 Guidelines for the treatment of intermediate-risk disease

Recommendations	Strength rating
Active surveillance (AS)	
Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA <10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP grade group 3 disease must be excluded from AS protocols.	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with intermediate-risk disease and a life expectancy of > 10 years.	Strong
Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong
Pelvic lymph node dissection (ePLND)	
Perform an ePLND in intermediate-risk disease based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2).	Strong
Radiotherapeutic treatment	
Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
For intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), use a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Strong

Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Weak
Offer high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plusIGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak

*6.2.3 **Treatment of high-risk localised disease***

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP [885]. When managed with non-curative intent, high-risk PCa is associated with 10-year and 15-year PCSM rates of 28.8 and 35.5%, respectively [886]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

6.2.3.1 Radical prostatectomy

Provided that the tumour is not fixed to the pelvic wall or there is no invasion of the urethral sphincter, RP is a reasonable option in selected patients with a low tumour volume. Extended PLND should be performed in all high-risk PCa cases [426, 427]. Patients should be aware pre-operatively that surgery may be part of multi-modal treatment, with adjuvant or salvage radiotherapy (SRT) or ADT. Neoadjuvant therapy using ADT with or without new generation hormone therapy or docetaxel is not indicated. (See Section 6.1.2.2.4) [542, 543]. Nerve sparing management is discussed in Section 6.1.2.3.6.

6.2.3.1.1 ISUP grade 4–5

The incidence of organ-confined disease is 26–31% in men with an ISUP grade ≥ 4 on systematic biopsy. A high rate of downgrading exists between the biopsy ISUP grade and the ISUP grade of the resected specimen [886]. Several retrospective case series have demonstrated CSS rates over 60% at 15 years after RP in the context of a multi-modal approach (adjuvant or salvage ADT and/or RT) in patients with a biopsy ISUP grade 5 [473, 549, 887, 888].

6.2.3.1.2 Prostate-specific antigen > 20 ng/mL

Reports in patients with a PSA > 20 ng/mL who underwent surgery as initial therapy within a multi-modal approach demonstrated a CSS at 15 years of over 70% [473, 549, 556, 889-891].

6.2.3.1.3 Radical prostatectomy in cN0 patients who are found to have pathologically confirmed LN invasion (pN1)

At 15 years follow-up cN0 patients who undergo RP but who were found to have pN1 were reported to have an overall CSS and OS of 45% and 42%, respectively [892-898]. A systematic review has reported 10-year BCR-free, CSS, and OS rates ranging from 28% to 56%, 72% to 98%, and 60% to 87.6%, respectively, in pN1 patients [899]. These findings highlight that pN1 patients represent a very heterogeneous patient group and further treatment must be individualised based on risk factors (see Sections 6.2.5.2 and 6.2.5.6).

6.2.3.2 External beam radiation therapy

For high-risk localised PCa, a combined modality approach should be used consisting of IMRT/VMAT plus long-term ADT. The duration of ADT has to take into account PS, co-morbidities and the number of poor prognostic factors. It is important to recognise that in several studies EBRT plus short-term ADT did not improve OS in high-risk localised PCa and long-term ADT (at least 2 to 3 years) is currently recommended for these patients [721, 722, 725].

6.2.3.2.1 Lymph node irradiation in cN0

There is low level evidence for prophylactic whole-pelvic irradiation as RCTs so far failed to show that patients benefit from prophylactic irradiation (46–50 Gy) of the pelvic LNs in intermediate- and high-risk disease [900-902].

The long-term results of the NRG/RTOG 9413-trial which randomised intermediate-risk and high-risk localised PCa patients (1,322 cN0 patients were enrolled), showed that neoadjuvant hormonal treatment plus whole pelvic RT improved PFS only compared with neoadjuvant ADT plus prostate RT and whole pelvic RT plus adjuvant ADT [903]. However, at the increased risk of ≥ grade 3 GI-toxicity. There was a suggestion of interaction between ADT and RT and therefore whole pelvic RT should be avoided without neoadjuvant ADT.

A well-conducted RCT compared prostate-only RT (PORT) vs. whole pelvic RT (WPRT) in localised high-risk- and locally advanced tumours (cN0) with a risk of > 20% of positive nodes (Roach formula). With a median follow-up of 68 months there was a significant improvement of distant metastasis-free survival (95.9% vs. 89.2%, HR: 0.35, p = 0.01) and DFS (89.5% vs.77.2%, p = 0.02). However, there was a significant higher rate of late GU ≥ 2 effects (17.7% vs. 7.5%, p = 0.02), the trial was relatively small in size with additional limitations and these findings are therefore insufficient to define a change in practice [904, 905]. The benefits of pelvic nodal irradiation using IMRT/VMAT merit further investigation in large scale RCTs as conducted by the RTOG or the UK National Cancer Research Institute (NCRI). Performing an ePLND in order to decide whether or not pelvic RT is required (in addition to combined prostate EBRT plus long-term ADT) remains experimental in the absence of high-level evidence.

6.2.3.2.2 Brachytherapy boost

In men with intermediate- or high-risk PCa, brachytherapy boost with supplemental EBRT and hormonal treatment may be considered. See Sections 6.1.3.4.1 and 6.1.3.4.2 for details on RCTs comparing EBRT alone and EBRT with LDR or HDR boost, respectively.

6.2.3.3 Options other than surgery or radiotherapy for the primary treatment of localised PCa

Currently there is a lack of evidence supporting any other treatment option apart from RP and radical RT in localised high-risk PCa. The use of ADT monotherapy was addressed by the EORTC 30891 trial [880] (see Section 6.2.4.4.2). Immediate ADT may only benefit patients with a PSA-DT < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour [880, 931].

6.2.3.4 Guidelines for radical treatment of high-risk localised disease

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to selected patients with high-risk localised PCa as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong
Radiotherapeutic treatment	
In patients with high-risk localised disease, use intensity-modulated radiation therapy (IMRT) /volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy to patients with high-risk localised disease.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

6.2.4 ***Treatment of locally advanced PCa***

In the absence of high-level evidence, a recent systematic review could not define the most optimal treatment option [906]. Randomised controlled trials are only available for EBRT. A local treatment combined with a systemic treatment provides the best outcome, provided the patient is ready and fit enough to receive both.

6.2.4.1 Radical prostatectomy

Surgery for locally advanced disease as part of a multi-modal therapy has been reported [886, 907, 908]. However, the comparative oncological effectiveness of RP as part of a multi-modal treatment strategy vs. upfront EBRT with ADT for locally advanced PCa remains unknown, although a prospective phase III RCT (SPCG-15)

comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally advanced (T3) disease is currently recruiting [909]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at 10 years [886, 907, 908, 910-914]. For cT3b–T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [915-917]. The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement (cN0). In case of suspected positive LNs during RP (initially considered cN0) the procedure should not be abandoned since RP may have a survival benefit in these patients. Intra-operative frozen section analysis is not justified in this case [604]. An ePLND is considered standard if a RP is planned.

6.2.4.2 Radiotherapy for locally advanced PCa

In locally advanced disease RCTs have clearly established that the additional use of long-term ADT combined with RT produces better OS than ADT or RT alone (see Section 6.1.3.1.4 and Tables 6.1.9 and 6.1.10) [906]. See Sections 6.1.3.4.1 and 6.1.3.4.2 for LDR and HDR brachytherapy boost in T3N0M0 PCa.

6.2.4.3 Treatment of cN1 M0 PCa

Lymph node metastasised PCa is where options for local therapy and systemic therapies overlap. Approximately 5% to 10% of newly diagnosed PCa patients have synchronous suspected pelvic nodal metastases on conventional imaging (CT/bone scan) without bone or visceral metastases (cN1 M0 stage). Meta-analyses have shown that PSMA-PET/CT prior to primary treatment in advanced PCa detected disease outside the prostate in 32% of cases despite prior negative conventional imaging using bone scan and pelvic CT/MRI [445]. A RCT assessing PSMA-PET/CT as staging tool in high-risk PCa confirmed these findings and showed a 32% increase in accuracy compared with conventional imaging for the detection of pelvic nodal metastases [465]. Notably, more sensitive imaging also causes a stage shift with more cases classified as cN1, but with, on average, lower nodal disease burden.

The management of cN1M0 PCa is mainly based on long-term ADT combined with a local treatment. The benefit of adding local treatment has been assessed in various retrospective studies, summarised in one systematic review [918] including 5 studies only [919-923]. The findings suggested an advantage in both OS and CSS after local treatment (RT or RP) combined with ADT as compared to ADT alone. The main limitations of this analysis were the lack of randomisation, of comparisons between RP and RT, as well as the value of the extent of PLND and of RT fields. Only limited evidence exists supporting RP for cN+ patients. Moschini *et al.*, compared the outcomes of 50 patients with cN+ with those of 252 patients with pN1, but cN0 at pre-operative staging. cN+ was not a significant predictor of CSS [924].

Based on the consistent benefit seen in retrospective studies including cN1 patients, local therapy is recommended in patients with cN1 disease at diagnosis in addition to long-term ADT (see Table 6.2.4.1).

The addition of a brachytherapy boost to ADT plus EBRT was not associated with improved OS in a retrospective study of 1,650 cN1 patients after multivariable adjustment and propensity score matching [925].

The intensification of systemic treatment (abiraterone acetate, docetaxel, zoledronic acid) has been assessed in unplanned sub-group analyses from the STAMPEDE multi-arm RCT by stratifying for cN+ and M+ status [40, 922]. The analyses were balanced for nodal involvement and for planned RT use in STAMPEDE at randomisation and at analysis. Abiraterone acetate was associated with a non-significant OS improvement (HR: 0.75, 95% CI: 0.48–1.18) in non-metastatic patients (N0/N+M0), but OS data were still immature with a low number of events. Furthermore, this was an underpowered subgroup analysis and hypothesis generating at best. Moreover, subgroup analyses were performed according to the metastatic/non-metastatic status and to the nodal status (any M) without specific data for the N+M0 population (n = 369; 20% of the overall cohort). The same would apply for the docetaxel arm in the STAMPEDE trial for which no specific subgroup analysis of newly diagnosed N+M0 PCa (n = 171, 14% of the overall cohort) was performed. However, the addition of docetaxel, zoledronic acid, or their combination, did not provide any OS benefit when stratifying by M0 and N+ status.

In the AFU-GETUG 12 trial comparing the impact of docetaxel plus estramustine in addition to ADT, 29% of included high-risk non-metastatic PCa patients had a nodal involvement at randomisation [926]. A non-significant trend towards better relapse survival rates was reported in the treatment arm (HR 0.66; 0.43–1.01) without OS benefit. A meta-analysis of docetaxel trials in N0M0-M1 patients concluded to an 8% 4-year survival advantage for docetaxel compared with ADT alone in terms of failure-free survival without OS benefit [927].

The STAMPEDE trial reported on 1,974 men with *de novo* high-risk/locally-advanced M0 disease, or relapse after primary curative therapy with high-risk features [928]. Eligibility criteria for *de novo* disease were: at least two of T-category clinical T3 or T4, Gleason sum score 8–10, PSA > 40 ng/mL, or node positive. Eligibility

criteria for relapsed patients were any of: node positive; PSA > 4 ng/mL and rising with a doubling time < 6 months; or PSA > 20 ng/mL. Patients were randomised to ADT alone, or ADT plus abiraterone, with or without enzalutamide. Radiotherapy was mandated for N0 disease and recommended for N1 disease. Androgen deprivation therapy was administered for 3 years, and abiraterone/enzalutamide for 2 years.

Four hundred and fifty-nine patients were treated with ADT plus abiraterone, and 527 with ADT plus abiraterone plus enzalutamide. Ninety-seven percent of patients randomised were treated for *de novo* disease. Thirty-nice percent of patients were N+. Radiotherapy was administered in 99% of N0 and 71% of cN1 patients, respectively. The primary outcome measure was metastasis-free survival. With a median follow-up of 72 months, the combination therapy significantly improved metastasis-free survival (HR 0.53, p = $2.9x10^{-11}$) and OS (HR: 0.60, p = $9.3x10^{-7}$). Adding enzalutamide did not improve efficacy. Combined ADT (for 3 years) and additional abiraterone (for 2 years), plus prostate and whole pelvic RT in the case of primary therapy, should be a SOC in this group of patients.

Table 6.2.4.1: Selected studies assessing local treatment in (any cT) cN1 M0 prostate cancer patients

Study	n	Design	Study period/ follow-up	Treatment arms	Effect on survival
Bryant, *et al*. 2018 [929]	648	Retrospective (National Veterans Affairs)	2000-2015 61 mo.	ADT ± EBRT	Significant benefit for combined treatment only if PSA levels less than the median (26 ng/mL) All-cause mortality HR: 0.50 CSS, HR: 0.38
Sarkar, *et al*. 2019 [930]	741	Retrospective (National Veterans Affairs)	2000-2015 51 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for RP All cause mortality HR 0.36 CSS, HR: 0.32 No statistical difference for RP vs. RT (p ≥ 0.1) All-cause mortality HR: 047 CSS, HR: 0.88
Lin, *et al*. 2015 [920]	983 before propensity score matching	Retrospective (NCDB)	2004-2006 48 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 73% vs. 52% HR: 0.5
Tward, *et al*. 2013 [919]	1,100	Retrospective (SEER)	1988-2006 64 mo.	EBRT (n = 397) vs. no EBRT (n=703) No information on ADT)	Significant benefit for EBRT 5-yr CSS 78% vs. 71% HR: 0.66 5-yr. OS: 68% vs. 56%, HR: 0.70
Rusthoven, *et al*. 2014 [923]	796	Retrospective (SEER)	1995-2005 61 mo.	EBRT vs. no EBRT (no information on ADT)	Significant benefit for EBRT 10-yr OS: 45% vs. 29% HR: 0.58
Seisen, *et al*. 2018 [921]	1,987	Retrospective (NCDB)	2003-2011 50 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for combined treatment 5-yr OS: 78.8% vs. 49.2% HR: 0.31 No difference between RP and RT
James, *et al*. 2016 [922]	177	Unplanned sub-group analysis RCT	2005-2014 17 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr OS: 93% vs. 71% 2-yr FFS: 81% vs 53% FFS, HR: 0.48

ADT = androgen deprivation therapy; CSS = cancer-specific survival; EBRT = external beam radiotherapy; FFS = failure-free survival; HR = hazard ratio; mo = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; yr = year.

6.2.4.4 Options other than surgery or radiotherapy for primary treatment

6.2.4.4.1 Investigational therapies

Currently cryotherapy, HIFU or focal therapies have no place in the management of locally-advanced PCa.

6.2.4.4.2 Androgen deprivation therapy monotherapy

The deferred use of ADT as single treatment modality has been answered by the EORTC 30891 trial [880]. Nine hundred and eighty-five patients with T0–4 N0–2 M0 PCa received ADT alone, either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS favoured immediate treatment (HR: 1.21, 95% CI: 1.05–1.39). Surprisingly, no different disease-free or symptom-free survival was observed, raising the question of survival benefit. In locally-advanced T3–T4 M0 disease unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50 ng/mL and a PSA-DT < 12 months or those that are symptomatic [880, 931]. The median time to start deferred treatment was 7 years. In the deferred treatment arm 25.6% of patients died without needing treatment.

6.2.4.5 Guidelines for radical treatment of locally-advanced disease

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to selected patients with locally-advanced PCa as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND prior to RP in locally-advanced PCa.	Strong
Radiotherapeutic treatments	
Offer patients with locally-advanced disease intensity-modulated radiation therapy (IMRT)/ volumetric modulated arc therapy (VMAT) plus image-guide radiation therapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer patients with locally advanced disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Offer long-term ADT for at least 2 years.	Strong
Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or ≥ 2 high-risk factors (cT3–4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong
Therapeutic options outside surgery or radiotherapy	
Do not offer whole gland treatment or focal treatment to patients with locally-advanced PCa.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Weak

6.2.5 ***Adjuvant treatment after radical prostatectomy***

6.2.5.1 Introduction

Adjuvant treatment is by definition additional to the primary or initial therapy with the aim of decreasing the risk of relapse. A post-operative detectable PSA is an indication of persistent prostate cells (see Section 6.2.6). All information listed below refers to patients with a post-operative undetectable PSA.

6.2.5.2 Risk factors for relapse

Patients with ISUP grade > 2 in combination with EPE (pT3a) and particularly those with SV invasion (pT3b) and/or positive surgical margins are at high risk of progression, which can be as high as 50% after 5 years [932]. Irrespective of the pT stage, the number of removed nodes [933-940], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [941]. A LN density (defined as 'the percentage of positive LNs in relation to the total number of analysed/removed LNs') of over 20% was found to be associated with poor prognosis [942]. The number of involved nodes seems to be a major factor for predicting relapse [935, 936, 943]; the threshold considered is less than 3 positive nodes from an ePLND [567, 935, 943]. However, prospective data are needed before defining a definitive threshold value.

6.2.5.2.1 Biomarker-based risk stratification after radical prostatectomy

The Decipher® gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment. A meta-analysis of five studies analysed the performance of the Decipher® Genomic Classifier (GC) test on men post-RP. The authors showed in multivariable analysis that Decipher® GC remained a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47, p < 0.001) per 0.1 unit increase in score and concluded that it can independently improve prognostication of patients post-RP within nearly all clinicopathologic, demographic, and treatment subgroups [944]. A systematic review of the evidence for the Decipher® GC has confirmed the clinical utility of this test in post-RP decision-making [945]. Further studies are needed to establish how to best incorporate Decipher® GC in clinical decision-making.

6.2.5.3 Immediate (adjuvant) post-operative external irradiation after RP (cN0 or pN0)

Four prospective RCTs have assessed the role of immediate post-operative RT (adjuvant RT [ART]), demonstrating an advantage (endpoint, development of BCR) in high-risk patients (e.g., pT2/pT3 with positive surgical margins and GS 8–10) post-RP (Table 6.2.5.1). In the ARO 96-02 trial, 80% of the pT3/R1/GS 8–10 patients randomised to observation developed BCR within 10 years. It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial which presents a major limitation interpreting these findings as patients with a detectable PSA would now be considered for salvage therapy rather than ART [946].

Table 6.2.5.1: Overview of all four randomised trials for adjuvant surgical bed radiation therapy after RP* (without ADT)

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [946]	431	pT3 cN0 ± involved SM	60-64 Gy vs. observation	> 0.4	152	10 yr.: 53% vs. 30% (p < 0.05)	**10 yr.: 74% vs. 66%** Median time: 15.2 vs. 13.3 yr., p = 0.023
EORTC 22911 2012 [947]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60 Gy vs. observation	> 0.2	127	10 yr.: 60.6% vs. 41% (p < 0.001)	**81% vs. 77% n.s.**
ARO 96-02 2014 [948]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60 Gy vs. observation	> 0.05 + confirmation	112	10 yr.: 56% vs. 35% (p = 0.0001)	**10 yr.: 82% vs. 86% n.s.**
FinnProstate Group 2019 [949]	250	pT2,R1/ pT3a	66.6 Gy vs. observation (+SRT)	> 0.4 (in 2 successive measurements)	112 vs. 103 (patients alive)	10 yr.: 82% vs. 61% p < 0.001	**10 yr.: 92% vs. 87% n.s.**

**See Section 6.3.5.1 for delayed (salvage) post-radical prostatectomy external irradiation.*
BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; n.s. = not significant; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin; SRT = salvage radiotherapy.

6.2.5.4 Comparison of adjuvant- and salvage radiotherapy

Two retrospective matched studies (510 and 149 patients receiving ART) failed to show an advantage for metastasis-free survival [950, 951]. However, both studies were underpowered for high-risk patients (pT3b/R1/ISUP grade 4–5 PCa).

In contrast to these studies, a propensity score-matched retrospective analysis of two cohorts of 366 pT3 and/or R1 patients found that compared to SRT at a PSA between 0.1 and 0.5 ng/mL, ART given at an undetectable PSA (< 0.1 ng/mL) improved all three endpoints; BCR, metastasis-free survival, and OS [952].

Both approaches (ART and early SRT) together with the efficacy of adjuvant ADT are compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial [953], the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial [954], and the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG-AFU 17) trial [955]. In addition, a pre-planned meta-analysis of all three trials has been published (Table 6.2.5.2) [956].

Two trials closed early after randomising 333/470 patients (RAVES) and 424/718 (GETUG-AFU-17) patients. RADICALS-RT included 1,396 patients with the option of subsequent inclusion in RADICALS-HT; 154/649 (24%) of patients starting in the adjuvant RT group also received neoadjuvant or adjuvant HT; 90 patients for 6 months/45 for 2 years/19 patients outside RADICALS-HT. From the SRT group, 61/228 (27%) received neoadjuvant or adjuvant HT for 6 months (n = 33) and 2 years (n = 13). Fifteen of these patients were treated outside the trial [953]. All men in the GETUG-AFU-17 trial (n = 424) received 6 months of HT. Alltogether, 684 out of 2,153 patients received additional ADT for at least 6 months across both trials [956]. Radiotherapy to the pelvic lymphatics was allowed in the GETUG-AFU and in the RADICALS-RT trials.

The primary endpoint for RAVES and GETUG-AFU 17 was biochemical PFS, and for RADICALS-RT metastasis-free survival. So far only PFS data has been reported, and not metastasis-free survival- or OS data. With a median follow-up between 4.9 years and 6.25 years there was no statistically significant difference for biochemical PFS for both treatments in all three trials (see Table 6.2.5.2) indicating that in the majority of patients adjuvant irradiation should be avoided. Additionally, there was a significant lower rate of grade ≥ 2 GU late side effects and grade 3–4 urethral strictures in favour of early SRT; which may also be caused by the low number of patients with PSA-progression and subsequent need for early SRT at the time of analysis (40% of patients).

It is important to note that the indication for ART changed over the last ten years with the introduction of ultra-sensitive PSA-tests, favouring early SRT. Therefore many patients, randomised in these 3 trials (accruing 2006–2008) are not likely to benefit from ART as there is a low risk of biochemical progression (~20–30%) in, for example, pT3R0 or pT2R1-tumours. The median pre-SRT PSA in all 3 trials was 0.24 ng/mL which is much lower than the conventional cut-off level of PSA < 0.5 ng/mL used to base ´early´ SRT on. Therefore, patients with 'low-risk factors' of biochemical progression after RP should be closely followed up with ultra-sensitive assays and SRT should be discussed as soon as PSA starts to rise, which has to be confirmed by a second PSA measurement (see Section 6.3). The proportion of patients with adverse pathology at RP (ISUP grade group 4–5 and pT3 with or without positive margins) in all 3 trials was low (between 10–20%) and therefore even the meta-analysis may be underpowered to show an outcome in favour of SRT [956]. In addition, the side-effect profile may have been impacted with a larger proportion of ART patients receiving treatment with older 3D-treatment planning techniques as compared to SRT patients (GETUG-AFU 17: ART, 69% 3D vs. 46% SRT) and patients treated more recently were more likely to undergo IMRT techniques with a proven lower rate of late side effects [665].

For these reasons, 10-year OS and metastasis-free survival endpoints results should be awaited before drawing final conclusions. Due to the small number of patients with adverse pathology (ISUP grade group 4–5 and pT3) included in these 3 trials (between 10–20%), ART remains a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients') i.e. ISUP grade group 4–5 and pT3 with or without positive margins [936, 957, 958]. This recommendation was supported by a published retrospective multi-centre study comparing ART and SRT in patients with high-risk features (pN1 or ISUP 4–5 and pT3/4-tumours) after RP [959]. After a median follow-up of 8.2 years of the 26,118 men included in the study, 2,104 patients died, 25.62% from PCa (n = 539) and 2,424 patients had adverse pathology compared with 23.694 who did not. After excluding men with persistent PSA after RP, ART when compared with early SRT showed a significantly lower acute mortality risk (p = 0.02, HR: 0.33).

Table 6.2.5.2 Overview of all three randomised trials and one meta-analysis for patients treated with adjuvant vs. early salvage RT after radical prostatectomy

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (yr)	BPFS	OS or MFS	Side effects
RAVES TROG 08.03/ ANZUP 2020 [954]	333 target was 470 early closed	pT3a/pT3b any T - SM+ PSA post-RP: < 0.1 ng/mL	64 Gy ART PSA: [< 0.1 ng/mL] vs. 64 Gy early SRT at PSA > 0.2 ng/mL med. pre-SRT: n.r.	> 0.4 post RT	6.1	**5 yr.: 86% vs. 87%** (p > 0.05)	n.r.	LT grade ≥ GU: 70% vs. 54% (p = 0.002)
RADICALS-RT 2020 [953]	1,396	pT3a/ pT3b/pT4 PSA > 10 ng/mL pre-RP any T, SM+ Gleason 7-10 PSA post-RP: < 0.2 ng/mL	52.5 Gy (20 Fx) or 66 Gy (33 Fx) ART early SRT identical at PSA > 0.1 med.pre-SRT: 0.2 ng/mL	> 0.4 or 2 at any time	4.9	**5 yr.: 85% vs. 88%** (p = 0.56)	n.r.	SR urinary incontinence 1 yr: 4.8 vs. 4 (p = 0.023) urethral stricture grade 3/4 2 yr: 6% vs. 4% (p = 0.02)
GETUG-AFU 17 2020 [955]	424 target was 718 early closed	pT3a/pT3b/ pT4a and SM+ PSA post-RP: < 0.1 ng/mL	66 Gy (ART) vs. 66 Gy early SRT at PSA 0.1 both groups: 6 mo. LHRH-A med. pre-SRT 0.24	> 0.4	6.25	**5 yr: 92% vs. 90%** (p = 0.42)	n.r.	LT grade ≥ 2 GU 27% vs. 7% (p < 0.001) ED: 28% vs. 8% (p < 0.001)
ARTISTIC-Meta-analysis 2020 [956]	2,153	see above	see above	see above	4.5	**5 yr.: 89% vs. 88%** p = 0.7	n.r.	n.r.

ART = adjuvant radiotherapy; BCR = biochemical recurrence; BPFS = biochemical progression-free survival; ED = erectile dysfunction; FU = follow-up; Fx = fraction; GU = genito-urinary; LHRH = luteinising hormone-releasing hormone; LT = late toxicity; mo = months; med = median; MFS = metastasis-free survival; n.r. = not reported; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SR = self reported; SRT = salvage radiotherapy; + = positive; yr = year.

6.2.5.5 Adjuvant androgen ablation in men with N0 disease

Adjuvant androgen ablation with bicalutamide 150 mg daily did not improve PFS in localised disease while it did for locally-advanced disease after RT. However, this never translated to an OS benefit [960]. A systematic review showed a possible benefit for PFS but not OS for adjuvant androgen ablation [542].

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (6 cycles) ended prematurely due to poor accrual. A phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally-advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [961]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [962].

6.2.5.6 Adjuvant treatment in pN1 disease

6.2.5.6.1 Adjuvant androgen ablation alone

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% and has been shown to significantly improve CSS and OS in prospective RCTs [963, 964]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics and these findings may not apply to men with less extensive nodal metastases.

6.2.5.6.2 Adjuvant radiotherapy combined with ADT in pN1 disease

In a retrospective multi-centre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated ‘adjuvantly‘ with continuous ADT (within 6 months after

surgery irrespective of PSA). The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), ISUP grade 2–5 and pT3–4 or R1, as well as men with 3 to 4 positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [965]. Comparable results were obtained from another retrospective single centre study [966]. These results were confirmed by a US National Cancer Database analysis based on 5,498 patients [967]. Another US National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT plus EBRT (including pelvic LNs) vs. observation and vs. ADT alone in all men with single or multiple adverse pathological features. Men without any adverse pathological features did not benefit from immediate adjuvant therapy [968].

In a series of 2,596 pN1 patients receiving ADT (n = 1,663) or ADT plus RT (n = 906), combined treatment was associated with improved OS, with a HR of 1.5 for ADT alone [969]. In a SEER retrospective population-based analysis, adding RT to RP showed a non-significant trend for improved OS but not PCa-specific survival, but data on the extent of additional RT is lacking in this study [923]. Radiotherapy should be given to the pelvic lymphatics and the prostatic fossa [965, 966, 970, 971]. In a systematic review of the literature, RT with or without ADT was associated with improved survival in men with locally-advanced disease and a higher number of positive nodes [899].

Retrospective data from a multi-centre cohort (1,491 pN1-patients after RP) with a median follow-up of 8.2 years, after excluding patients with persisting PSA, show a significantly lower all-cause mortality risk for adjuvant RT compared with early SRT (p = 0.04, HR: 0.66). No data are available in pN1 patients addressing adjuvant EBRT without ADT [972].

6.2.5.6.3 Observation of pN1 patients after radical prostatectomy and extended lymph node dissection

Several retrospective studies and a systematic review addressed the management of patients with pN1 PCa at RP [899, 943, 965, 966, 973]. A subset of patients with limited nodal disease (1–2 positive LNs) showed favourable oncological outcomes and did not require additional treatment.

An analysis of 209 pN1 patients with one or two positive LNs at RP showed that 37% remained metastasis-free without need of salvage treatment at a median follow-up of 60.2 months [973]. Touijer *et al*., reported their results of 369 LN-positive patients (40 with and 329 without adjuvant treatment) and showed that higher pathologic grade group and ≥ 3 positive LNs were significantly associated with an increased risk of BCR on multivariable analysis [943]. Biochemical-free survival rates in pN1 patients without adjuvant treatment ranged from 43% at 4 years to 28% at 10 years [899]. Reported CSS rates were 78% at 5 years and 72% at 10 years. The majority of these patients were managed with initial observation after surgery, had favourable disease characteristics, and 63% had only one positive node [899]. Initial observation followed by early salvage treatment at the time of recurrence may represent a safe option in selected patients with a low disease burden [899].

6.2.5.7 Guidelines for adjuvant treatment in pN0 and pN1 disease after radical prostatectomy

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) in pN0 patients.	Strong
Only offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) to high-risk patients (pN0) with adverse pathology (ISUP grade group 4–5 and pT3 with or without positive margins).	Strong
Discuss three management options with patients with pN1 disease after an extended lymph node dissection, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak

6.2.5.8 Guidelines for non-curative or palliative treatments in prostate cancer

Recommendations	Strength rating
Watchful waiting (WW) for localised prostate cancer	
Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong

Watchful waiting for locally-advanced prostate cancer	
Offer a deferred treatment policy using androgen deprivation monotherapy to M0 asymptomatic patients with a prostate-specific antigen (PSA) doubling time > 12 months, a PSA < 50 ng/mL and well-differentiated tumour, who are unwilling or unable to receive any form of local treatment.	Weak

*6.2.6 **Persistent PSA after radical prostatectomy***

Between 5 and 20% of men continue to have detectable or persistent PSA after RP (when defined in the majority of studies as detectable post-RP PSA of ≥ 0.1 ng/mL within 4 to 8 weeks of surgery) [974, 975]. It may result from persistent local disease, pre-existing metastases or residual benign prostate tissue.

6.2.6.1 Natural history of persistently elevated PSA after RP

Several studies have shown that persistent PSA after RP is associated with more advanced disease (such as positive surgical margins, pathologic stage ≥ T3a, positive nodal status and/or pathologic ISUP grade > 3) and poor prognosis. Initially defined as ≥ 0.1 ng/mL, improvements in the sensitivity of PSA assays now allow for the detection of PSA at much lower levels.

Moreira *et al*., demonstrated that failure to achieve a PSA of less than 0.03 ng/mL within 6 months of surgery was associated with an increased risk of BCR and overall mortality [976, 977]. However, since the majority of the published literature is based on the 0.1 ng/mL PSA cut-off, there is significantly more long-term data for this definition. Predictors of PSA persistence were higher BMI, higher pre-operative PSA and ISUP grade ≥ 3 [977]. In patients with PSA persistence, one and 5-year BCR-free survival were 68% and 36%, compared to 95% and 72%, respectively, in men without PSA persistence [976]. Ten-year OS in patients with and without PSA persistence was 63% and 80%, respectively.

Spratt *et al*., confirmed that a persistently detectable PSA after RP represents one of the worst prognostic factors associated with oncological outcome [978]. Of 150 patients with a persistent PSA, 95% received RT before detectable metastasis. In a multivariable analysis the presence of a persistently detectable PSA post-RP was associated with a 4-fold increase in the risk of developing metastasis. This was confirmed by data from Preisser *et al*., who showed that persistent PSA is prognostic of an increased risk of metastasis and death [979]. At 15 years after RP, metastasis-free survival rates, OS and CSS rates were 53.0 vs. 93.2% ($p < 0.001$), 64.7 vs. 81.2% ($p < 0.001$) and 75.5 vs. 96.2% ($p < 0.001$) for persistent vs. undetectable PSA, respectively. The median follow-up was 61.8 months for patients with undetectable PSA vs. 46.4 months for patients with persistent PSA. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR: 3.59, $p < 0.001$), death (HR: 1.86, $p < 0.001$) and cancer-specific death (HR: 3.15, $p < 0.001$).

However, not all patients with persistent PSA after RP experience disease recurrence. Xiang *et al*., showed a 50% 5-year BCR-free survival in men who had a persistent PSA level > 0.1 but ≤ 0.2 ng/mL at 6–8 weeks after RP [980].

Rogers *et al*., assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [981]. No patient received adjuvant therapy before documented metastasis. In their study, 38% of patients had no evidence of metastases for ≥ 7 years while 32% of the patients were reported to develop metastases within 3 years. Noteworthy is that a significant proportion of patients had low-risk disease. In multivariable analysis the PSA slope after RP (as calculated using PSA levels 3 to 12 months after surgery) and pathological ISUP grade were significantly associated with the development of distant metastases.

6.2.6.2 Imaging in patients with persistently elevated PSA after RP

Standard imaging with bone scan and MRI has a low pick-up rate in men with a PSA below 2 ng/mL. However, PSMA PET/CT has been shown to identify residual cancer with positivity rates of 33%, 46%, 57%, 82%, and 97%, in men with post-RP PSA ranges of 0–0.19, 0.2–0.49, 0.5–0.99, 1–1.99, and ≥ 2 ng/mL, respectively [982-987] which can guide SRT planning [988]. Based on these post-RP PSA ranges, Schmidt-Hegemann *et al*., studied 129 patients who had either persistent PSA (52%) or BCR (48%) after RP, showing that men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those developing a detectable PSA [989]. In a multi-centre retrospective study including 191 patients, ^{68}Ga-PSM localised biochemical persistence after RP in more than two-thirds of patients with high-risk PCa features. The obturator and presacral/mesorectal nodes were identified as high risk for residual disease [990]. Another retrospective study included 150 patients with persistent PSA after RARP who were re-staged with both ^{68}Ga-PSMA and ^{18}F-DCFPyL PSMA. The authors found that in the presence of persistent PSA the majority of patients already had metastatic pelvic LNs or distant metastases which would support a role of PSMA PET/CT imaging in guiding (salvage) treatment strategies [991]. At present there is uncertainty regarding the best treatment if PSMA PET/CT shows metastatic disease.

6.2.6.3 *Impact of post-operative RT and/or ADT in patients with persistent PSA*

The benefit of SRT in patients with persistent PSA remains unclear due to a lack of RCTs, however, it would appear that men with a persistent PSA do less well than men with BCR undergoing RT.

Preisser *et al*., compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not [979]. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between patients with SRT vs. no RT, OS rates at 10 years after RP were 86.6 vs. 72.6% in the entire cohort ($p < 0.01$), 86.3 vs. 60.0% in patients with positive surgical margin ($p = 0.02$), 77.8 vs. 49.0% in pT3b disease ($p < 0.001$), 79.3 vs. 55.8% in ISUP grade 1 disease ($p < 0.01$) and 87.4 vs. 50.5% in pN1 disease ($p < 0.01$), respectively. Moreover, CSS rates at 10 years after RP were 93.7 vs. 81.6% in the entire cohort ($p < 0.01$), 90.8 vs. 69.7% in patients with positive surgical margin ($p = 0.04$), 82.7 vs. 55.3% in pT3b disease ($p < 0.01$), 85.4 vs. 69.7% in ISUP grade 1 disease ($p < 0.01$) and 96.2 vs. 55.8% in pN1 disease ($p < 0.01$), for SRT vs. no RT, respectively. In multivariable models, after 1:1 propensity score matching, SRT was associated with lower risk for death (HR: 0.42, $p = 0.02$) and lower cancer-specific death (HR: 0.29, $p = 0.03$). These survival outcomes in patients with persistent PSA who underwent SRT suggest they benefit but outcomes are worse than for men experiencing BCR [992].

It is clear from a number of studies that poor outcomes are driven by the level of pre-RT PSA, the presence of ISUP grade ≥ 4 in the RP histology and pT3b disease [993-998]. Fossati *et al*., suggested that only men with a persistent PSA after RP and ISUP grade ≤ 3 benefit significantly [999], although this is not supported by Preisser *et al*. [979]. The current data do not allow making any clear treatment decisions.

Addition of ADT may improve PFS [994]. Choo *et al*., studied the addition of 2-year ADT to immediate RT to the prostate bed in patients with pathologic T3 disease (pT3) and/or positive surgical margins after RP [994]. Twenty-nine of the 78 included patients had persistently detectable post-operative PSA. The relapse-free rate was 85% at 5 years and 68% at 7 years, which was superior to the 5-year progression-free estimates of 74% and 61% in the post-operative RT arms of the EORTC and the SWOG studies, respectively, which included patients with undetectable PSA after RP [946, 947]. Patients with persistently detectable post-operative PSA comprised approximately 50% and 12%, respectively, of the study cohorts in the EORTC and the SWOG studies.

In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only (66 Gy per protocol [arm C]). The 10-year clinical relapse-free survival was 63% [993]. The GETUG-22 trial comparing RT with RT plus short-term ADT for post-RP PSA persistence (0.2–2.0 ng/mL) reported good tolerability of the combined treatment. The oncological endpoints are yet to be published [1000].

Two systematic reviews addressing persistent PSA confirmed a strong correlation of PSA persistence with poor oncologic outcomes [974, 975]. Ploussard *et al*., also reported that SRT was associated with improved survival outcomes, although the available evidence is of low quality [975].

6.2.6.4 *Conclusion*

The available data suggest that patients with PSA persistence after RP may benefit from early aggressive multi-modality treatment, however, the lack of prospective RCTs makes firm recommendations difficult.

6.2.6.5 *Recommendations for the management of persistent PSA after radical prostatectomy*

Recommendations	Strength rating
Offer a prostate-specific membrane antigen positron-emission tomography (PSMA PET) scan to men with a persistent prostate-specific antigen > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak
Treat men with no evidence of metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.3 Management of PSA-only recurrence after treatment with curative intent

Follow-up will be addressed in Chapter 7 and is not discussed in this section.

6.3.1 *Background*

Between 27% and 53% of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily

lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding over-treating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.3.2 Controversies in the definitions of clinically relevant PSA relapse

The PSA level that defines treatment failure depends on the primary treatment. Patients with rising PSA after RP or primary RT have different risks of subsequent symptomatic metastatic disease based on various parameters, including the PSA level. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments.

After RP, the threshold that best predicts further metastases is a PSA > 0.4 ng/mL and rising [1001-1003]. However, with access to ultra-sensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients.

After primary RT, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is 'any PSA increase > 2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir' [1004]. Clinicians should interpret a PSA rise in light of the EAU BCR risk groups (see Section 6.3.3).

After HIFU or cryotherapy no endpoints have been validated against clinical progression or survival; therefore, it is not possible to give a firm recommendation of an acceptable PSA threshold after these alternative local treatments [1005].

6.3.3 Natural history of biochemical recurrence

Once a PSA recurrence has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. A systematic review and meta-analysis investigated the impact of BCR on hard endpoints and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, PCa-specific and overall mortality [1005]. However, the effect size of BCR as a risk factor for mortality is highly variable. After primary RP its impact ranges from HR 1.03 (95% CI: 1.004–1.06) to HR 2.32 (95% CI: 1.45–3.71) [1006, 1007]. After primary RT, OS rates are approximately 20% lower at 8 to 10 years follow-up even in men with minimal co-morbidity [1008, 1009]. Still, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality.

The risk of subsequent metastases, PCa-specific- and overall mortality may be predicted by the initial clinical and pathologic factors (e.g., T-category, PSA, ISUP grade) and PSA kinetics (PSA-DT and interval to PSA failure), which was further investigated by the systematic review [1005].

For patients with BCR after RP, the following outcomes were found to be associated with significant prognostic factors:

- distant metastatic recurrence: positive surgical margins, high RP specimen pathological ISUP grade, high pT category, short PSA-DT, high pre-SRT PSA;
- prostate-cancer-specific mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure as defined by investigators, short PSA-DT;
- overall mortality: high RP specimen pathological ISUP grade, short interval to biochemical failure, high PSA-DT.

For patients with BCR after RT, the corresponding outcomes are:

- distant metastatic recurrence: high biopsy ISUP grade, high cT category, short interval to biochemical failure;
- prostate-cancer-specific mortality: short interval to biochemical failure;
- overall mortality: high age, high biopsy ISUP grade, short interval to biochemical failure, high initial (pre-treatment) PSA.

Based on this meta-analysis, proposal is to stratify patients into 'EAU Low-Risk BCR' (PSA-DT > 1 year AND pathological ISUP grade < 4 for RP; interval to biochemical failure > 18 months AND biopsy ISUP grade < 4 for RT) or 'EAU High-Risk BCR' (PSA-DT < 1 year OR pathological ISUP grade 4–5 for RP, interval to biochemical failure < 18 months OR biopsy ISUP grade 4–5 for RT), since not all patients with BCR will have similar outcomes. The stratification into 'EAU Low-Risk' or 'EAU High-Risk' BCR has recently been validated in a European cohort [1010].

*6.3.4 **The role of imaging in PSA-only recurrence***

Imaging is only of value if it leads to a treatment change which results in an improved outcome. In practice, however, there are very limited data available regarding the outcomes consequent on imaging at recurrence.

6.3.4.1 Assessment of metastases

6.3.4.1.1 Bone scan and abdominopelvic CT

Because BCR after RP or RT precedes clinical metastases by 7 to 8 years on average [937, 1011], the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [1012]. In men with PSA-only recurrence after RP the probability of a positive bone scan is < 5%, when the PSA level is < 7 ng/mL [1013, 1014]. Only 11–14% of patients with BCR after RP have a positive CT [1013]. In a series of 132 men with BCR after RP the mean PSA level and PSA velocity associated with a positive CT were 27.4 ng/mL and 1.8 ng/mL/month, respectively [1015].

6.3.4.1.2 Choline PET/CT

In two different meta-analyses the combined sensitivities and specificities of choline PET/CT for all sites of recurrence in patients with BCR were 86–89% and 89–93%, respectively [1016, 1017].

Choline PET/CT may detect multiple bone metastases in patients showing a single metastasis on bone scan [1018] and may be positive for bone metastases in up to 15% of patients with BCR after RP and negative bone scan [1019]. The specificity of choline PET/CT is also higher than bone scan with fewer false-positive and indeterminate findings [450]. Detection of LN metastases using choline PET/CT remains limited by the relatively poor sensitivity of the technique (see Section 5.3.2.3). Choline PET/CT sensitivity is strongly dependent on the PSA level and kinetics [459, 1020, 1021]. In patients with BCR after RP, PET/CT detection rates are only 5–24% when the PSA level is < 1 ng/mL but rises to 67–100% when the PSA level is > 5 ng/mL. Despite its limitations, choline PET/CT may change medical management in 18–48% of patients with BCR after primary treatment [1022-1024].

Choline PET/CT should only be recommended in patients fit enough for curative loco-regional salvage treatment.

6.3.4.1.3 Fluoride PET and PET/CT

^{18}F-NaF PET/CT has a higher sensitivity than bone scan in detecting bone metastases [1025]. However, ^{18}F-NaF PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [1026].

6.3.4.1.4 Fluciclovine PET/CT

^{18}F-Fluciclovine PET/CT has been approved in the U.S. and Europe and it is therefore one of the PCa-specific radiotracers widely commercially available [1027-1029].

18F-Fluciclovine PET/CT has a slightly higher sensitivity than choline PET/CT in detecting the site of relapse in BCR [1030]. In a multi-centre trial evaluating 596 patients with BCR in a mixed population (33.3% after RP, 59.5% after RT ± RP, 7.1% other) fluciclovine PET/CT showed an overall detection rate of 67.7%; lesions could be visualised either at local level (38.7%) or in LNs and bones (9%) [1031]. As for choline PET/CT, fluciclovine PET/CT sensitivity is dependent on the PSA level, with a sensitivity likely inferior to 50% at PSA < 1 ng/mL.

In a prospective RCT evaluating the impact of ^{18}F-fluciclovine PET/CT on SRT management decisions in patients with recurrence post-prostatectomy, in 28 of 79 (35.4%) patients overall radiotherapeutic management changed following ^{18}F-fluciclovine PET/CT [1032]. ^{18}F-Fluciclovine PET/CT had a significantly higher positivity rate than conventional imaging (abdominopelvic CT or MRI plus bone scan) for whole body (79.7% vs. 13.9%, $p < 0.001$), prostate bed (69.6% vs. 5.1%, $p < 0.001$), and pelvic LNs (38.0% vs. 10.1%, $p < 0.001$) [1032]. However, as yet, no data demonstrating that these changes translate into a survival benefit are available.

6.3.4.1.5 Prostate-specific membrane antigen based PET/CT

Prostate-specific membrane antigen PET/CT has shown good potential in patients with BCR, although most studies are limited by their retrospective design. Reported predictors of ^{68}Ga-PSMA PET in the recurrence setting were recently updated based on a high-volume series (see Table 6.3.1) [982]. High sensitivity (75%) and specificity (99%) were observed on per-lesion analysis.

Table 6.3.1: PSMA-positivity separated by PSA level category [982]

PSA (ng/mL)	^{68}Ga-PMSA PET positivity
< 0.2	33% (CI: 16–51)
02–0.49	45% (CI: 39–52)
0.5–0.99	59% (CI: 50–68)
1.0–1.99	75% (CI: 66–84)
2.0+	95% (CI: 92–97)

PSA = prostate-specific antigen; ^{68}Ga-PSMA PET = Gallium-68 prostate-specific membrane antigen positron emission tomography.

Prostate-specific membrane antigen PET/CT seems substantially more sensitive than choline PET/CT, especially for PSA levels < 1 ng/mL [1033, 1034]. In a study of 314 patients with BCR after treatment and a median PSA level of 0.83 ng/mL, ^{68}Ga-PSMA PET/CT was positive in 197 patients (67%) [1035]. In another prospective multi-centre trial including 635 patients with BCR after RP (41%), RT (27%), or both (32%), PPV for ^{68}Ga-PSMA PET/CT was 0.84 (95% CI: 0.75–0.90) by histopathologic validation (primary endpoint, n = 87) and 0.92 (95% CI: 0.75–0.90) by a composite reference standard. Detection rates significantly increased with PSA value [1036].

A prospective multi-centre, multi-reader, open-label, phase II/III trial (OSPREY) evaluated the diagnostic performance of ^{18}F-DCFPyL in patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging [444]. Median sensitivity and median PPV 95.8% (95% CI: 87.8%–99.0%) and 81.9% (95% CI: 73.7%–90.2%), respectively.

Another prospective study evaluated the diagnostic performance of ^{18}F-DCFPyL in 208 men with BCR after RP or RT. The primary endpoint, the correct localisation rate was achieved, demonstrating positive findings on DCFPyL PET/CT in the setting of negative standard imaging [1037]. At present there are no conclusive data about comparison of such tracers [1038].

6.3.4.1.6 Whole-body and axial MRI

Whole body MRI has not been widely evaluated in BCR because of its limited value in the detection of early metastatic involvement in normal-sized LNs [461, 1039]. In a prospective series of 68 patients with BCR, the diagnostic performance of DW-MRI was significantly lower than that of ^{68}Ga-PSMA PET/CT and ^{18}NaF PET/CT for diagnosing bone metastases [1040].

6.3.4.2 Assessment of local recurrences

6.3.4.2.1 Local recurrence after radical prostatectomy

Because the sensitivity of anastomotic biopsies is low, especially for PSA levels < 1 ng/mL [1012], salvage RT is usually decided on the basis of BCR without histological proof of local recurrence. The dose delivered to the prostatic fossa tends to be uniform since it has not been demonstrated that a focal dose escalation at the site of recurrence improves the outcome. Therefore, most patients undergo salvage RT without local imaging.

Magnetic resonance imaging can detect local recurrences in the prostatic bed but its sensitivity in patients with a PSA level < 0.5 ng/mL remains controversial [1041, 1042]. Choline PET/CT is less sensitive than MRI when the PSA level is < 1 ng/mL [1043]. In a retrospective study of 53 patients with BCR after RP (median PSA level 1.5 ng/mL) who underwent ^{18}F-choline whole body hybrid PET/MRI, MRI identified more local relapses while PET detected more regional and distant metastases [1044].

The detection rates of ^{68}Ga-PSMA PET/CT in patients with BCR after RP increase with the PSA level [1045]. Prostate-specific membrane antigen PET/CT studies showed that a substantial part of recurrences after RP were located outside the prostatic fossa even at low PSA levels [983, 1046]. Combining ^{68}Ga-PSMA PET and MRI may improve the detection of local recurrences, as compared to ^{68}Ga-PSMA PET/CT [1047-1049].

The EMPIRE-1, a single-centre, open-label, phase II/III RCT evaluated the role of ^{18}F-fluciclovine-PET/CT compared with conventional imaging for salvage RT. Three hundred and sixty five patients with detectable PSA after RP, but negative results on conventional imaging were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow-up was 3.5 years. In adjusted analyses, the study group was significantly associated with event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1050].

6.3.4.2.2 Local recurrence after radiation therapy

In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained 18–24 months after initial treatment. Given the morbidity of local salvage options it is necessary to obtain histological proof of the local recurrence before treating the patient [1012].

Transrectal US is not reliable in identifying local recurrence after RT. In contrast, MRI has yielded excellent results and can be used for biopsy targeting and guiding local salvage treatment [1012, 1051-1054], even if it slightly underestimates the volume of the local recurrence [1055]. Detection of recurrent cancer is also feasible with choline PET/CT [1056], but choline PET/CT has not yet been compared to MRI. Prostate-specific membrane antigen PET/CT can also play a role in the detection of local recurrences after RT [982].

6.3.4.3 Summary of evidence on imaging in case of biochemical recurrence

In patients with BCR imaging can detect both local recurrences and distant metastases, however, the sensitivity of detection depends on the PSA level. After RP, PSMA PET/CT seems to be the imaging modality with the highest sensitivity at low PSA levels (< 0.5 ng/mL) and may help distinguishing patients with recurrences confined to the prostatic fossa from those with distant metastases which may impact the design and use of post-RP salvage RT. After RT, MRI has shown excellent results at detecting local recurrences and guiding prostate biopsy. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences and who are fit for these salvage therapies. Choline-, fluciclovine- or PSMA-PET/CT can be used to detect metastases in these patients but for this indication PSMA PET/CT seems the most sensitive technique.

6.3.4.4 Summary of evidence and guidelines for imaging in patients with biochemical recurrence

Recommendations	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography (PET) computed tomography (CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions.	Weak
In case PSMA PET/CT is not available, and the PSA level is ≥ 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions.	Weak
PSA recurrence after radiotherapy	
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak
Perform PSMA PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment.	Strong

*6.3.5 **Treatment of PSA-only recurrences***

The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

6.3.5.1 Treatment of PSA-only recurrences after radical prostatectomy

6.3.5.1.1 Salvage radiotherapy for PSA-only recurrence after radical prostatectomy (cTxcN0M0, without PET/CT)

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al*., reported a 75% reduced risk of systemic progression with SRT when comparing 856 SRT patients with 1,801 non-SRT patients [1057]. The RAVES and RADICAL trials assessing SRT in post-RP patients with PSA levels exceeding 0.1–0.2 ng/mL showed 5-year freedom from BCR and BCR-free survival rates of 88% [953, 1058].

The PSA level at BCR was shown to be prognostic [1057]. More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level [1059-1062], corresponding to a ~80% chance of being progression-free 5 years later [1063]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or salvage RT alone (n = 160) within 2 years of BCR showed that salvage RT was associated with a 3-fold increase in PCa-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage RT has been shown to be effective mainly in patients with a short PSA-DT [1064].

The EAU BCR definitions have been externally validated and may be helpful for individualised treatment decisions [1010]. Despite the indication for salvage RT, a ‘wait and see‘ strategy remains an option for the EAU BCR ‘Low-Risk’ group [1005, 1065]. For an overview see Table 6.3.2.

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence; metastatic disease, disease-specific and OS are more meaningful endpoints to support clinical decision-making. A systematic review and meta-analysis on the impact of BCR after RP reports SRT to be favourable for OS and PCa-specific mortality. In particular SRT should be initiated in patients with rapid PSA kinetics after RP and with a PSA cut-off of 0.4 ng/mL [1005]. An international multi-institutional analysis of pooled data from RCTs has suggested that metastasis-free survival is the most valid surrogate endpoint with respect to impact on OS [1066, 1067]. Table 6.3.3 summarises results of recent studies on clinical endpoints after SRT.

Table 6.3.2: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy PSA level* (cTxcN0M0, without PET/CT)

Study	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, *et al.* 2018 [1068]	464	71	0.31	66.6 Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2 ng/mL p < 0.0001
Soto, *et al.* 2012 [1069]	441	36	< 1 (58%)	68 Gy 24% ADT	63/55% (3) ADT/no ADT	44/40% ADT/no ADT p < 0.16
Stish, *et al.* 2016 [1059]	1,106	107	0.6	68 Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5 ng/mL p < 0.001
Tendulkar, *et al.* 2016 [1070]	2,460	60	0.5	66 Gy 16% ADT	56% (5)	Pre-SRT PSA 71% 0.01–0.2 ng/mL 63% 0.21–0.5 ng/mL 54% 0.51–1.0 ng/mL 43% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

**Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival'. To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.*
ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up; mo = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen; SRT = salvage radiotherapy; yr = year.

Table 6.3.3: Recent studies reporting clinical endpoints after SRT (cTxcN0M0, without PET/CT) (the majority of included patients did not receive ADT)

Study	n	Median FU (mo)	Regimen	Outcome
Bartkowiak, *et al.* 2018 [1068]	464	71	66.6 (59.4-72) Gy no ADT	5.9 yr. OS post-SRT PSA < 0.1 ng/mL 98% post-SRT PSA ≥ 0.1 ng/mL 92% p = 0.005
Jackson, *et al.* 2014 [1071]	448	64	68.4 Gy no ADT	5 yr. DM post-SRT PSA < 0.1 ng/mL 5% post-SRT PSA ≥ 0.1 ng/mL 29% p < 0.0001 5 yr. DSM post-SRT PSA < 0.1 ng/mL 2% post-SRT PSA ≥ 0.1 ng/mL 7% p < 0.0001 OS post-SRT PSA < 0.1 ng/mL 97% post-SRT PSA ≥ 0.1 ng/mL 90% p < 0.0001

Stish, *et al.* 2016 [1059]	1,106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr. DM SRT: PSA ≤ 0.5 ng/mL 7% and 12% SRT: PSA > 0.5 ng/mL 14% and 23% p < 0.001 5 and 8.9 yr. DSM SRT: PSA ≤ 0.5 ng/mL < 1% and 6% SRT: PSA > 0.5 ng/mL 5% and 10% p = 0.02 5 and 8.9 yr. OS SRT: PSA ≤ 0.5 ng/mL 94% and 86% SRT: PSA > 0.5 ng/mL 91% and 78% p = 0.14
Tendulkar, *et al.* 2016 [1070]	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10-yr. DM (19% all patients) Pre-SRT PSA 9% 0.01–0.2 ng/mL 15% 0.21–0.5 ng/mL 19% 0.51–1.0 ng/mL 20% 1.01–2.0 ng/mL 37% > 2.0 ng/mL p < 0.001

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; FU = follow up; mo. = month; n = number of patients; OS = overall survival; PSA = prostate specific antigen; SRT = salvage radiotherapy.

6.3.5.1.2 Salvage radiotherapy combined with androgen deprivation therapy (cTxcN0, without PET/CT)

Data from RTOG 9601 suggest both CSS and OS benefit when adding 2 years of bicalutamide (150 mg o.d.) to SRT [1072]. According to GETUG-AFU 16 also 6-months treatment with a LHRH-analogue can significantly improve 10-year BCR, biochemical PFS and, modestly, metastasis-free survival. However, SRT combined with either goserelin or placebo showed similar DSS and OS rates [1073]. Table 6.3.4 provides an overview of these two RCTs.

These RCTs support adding ADT to SRT. However, when interpreting these data it has to be kept in mind that RTOG 9601 used outdated radiation dosages (< 66 Gy) and technique. The question with respect to the patient risk profile, whether to offer combination treatment or not and the optimal combination (LHRH or bicalutamide) remains, as yet, unsolved. The EAU BCR risk classification may offer guidance in this respect [1005, 1010].

One of these RCTs reports improved OS (RTOG 96-01) and the other improved metastasis-free survival but due to methodological discrepancies also related to follow-up and risk patterns, it is, as yet, not evident which patients should receive ADT, which type of ADT, and for how long. Men at high risk of further progression (e.g., with a PSA ≥ 0.7 ng/mL and GS ≥ 8) may benefit from SRT combined with two years of ADT; for those at lower risk (e.g., PSA < 0.7 ng/mL and GS = 8) SRT combined with 6 months of ADT may be sufficient. Men with a low-risk profile (PSA < 0.5 ng/mL and GS < 8) may receive SRT alone. In a sub-analysis of men with a PSA of 0.61 to 1.5 (n = 253) there was an OS benefit associated with anti-androgen assignment (HR: 0.61, 95% CI: 0.39–0.94). In those receiving early SRT (PSA 0.6 ng/mL, n = 389), there was no improvement in OS (HR: 1.16, 95% CI: 0.79–1.70), with increased other-cause mortality (sub-distribution HR: 1.94, 95% CI: 1.17–3.20, p = 0.01) and increased odds of late grades 3–5 cardiac and neurologic toxic side-effects (OR: 3.57, 95% CI: 1.09–15.97, p = 0.05). These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of anti-androgen treatment with SRT. In patients receiving late SRT (PSA > 0.6 ng/mL), hormone therapy was associated with improved outcomes. In men receiving early SRT (PSA < 0.6 ng/mL), long-term anti-androgen treatment was not associated with improved OS [1074].

A review addressing the benefit from combining HT with SRT suggested risk stratification of patients based on the pre-SRT PSA (< 0.5, 0.6–1, > 1 ng/mL), margin status and ISUP grade as a framework to individualise treatment [1075]. In a retrospective multi-centre-study including 525 patients, only in patients with more aggressive disease characteristics (pT3b/4 and ISUP grade > 4 or pT3b/4 and PSA at early SRT > 0.4 ng/mL) the administration of concomitant ADT was associated with a reduction in distant metastasis [1076]. Similarly, in a retrospective analysis of 1,125 patients, stage ≥ pT3b, GS ≥ 8 and a PSA level at SRT > 5 ng/mL were identified as risk factors for clinical recurrence. A significant effect of long-term ADT was observed in patients with ≥ 2 adverse features. For patients with a single risk factor, short-term HT was sufficient whilst patients without risk factors showed no significant benefit from concomitant ADT [1077].

Table 6.3.4: Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone

Study	n	Risk groups	Median FU (mo)	Regimen	Outcome
GETUG-AFU 16 2019 [1073]	369 RT + ADT 374 RT	ISUP grade ≤ 2/3 89% ISUP grade ≥ 4 11% cN0	112	66 Gy + 6 mo. GnRH analogue 6 mo. 66 Gy	**10-yr.** **PFS: RT + ADT, 64%** **PFS: RT, 49%** p < 0.0001 **MFS: RT + ADT, 75%** **MFS: RT, 69%** p = 0.034
RTOG 9601 2017 [1072]	384 RT + ADT 376 RT	pT2 R1, pT3 cN0	156	64.8 Gy + bicalutamide 24 mo. 64.8 Gy + placebo	**12-yr.** **cumulative DM** **RT + ADT: 14%** **RT + placebo: 23%** p = 0.005 **OS** **RT + ADT: 76%** **RT + placebo: 71%** p = 0.04 **DSM** **RT + ADT: 5.8%** **RT + placebo: 13.4%** p < 0.001

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; PFS = progression free survival; FU = follow-up; GnRH = gonadotropin-releasing hormone; MFS = metastasis-free survival; OS = overall survival; PFS = progression-free survival; mo = months; n = number of patients; RT = radiotherapy; yr = year.

6.3.5.1.2.1 Target volume, dose, toxicity

There have been various attempts to define common outlines for ‘clinical target volumes‘ of PCa [1078-1081] and for organs at risk of normal tissue complications [1082]. However, given the variations of techniques and dose-constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS but not metastasis-free survival has been reported in patients receiving whole pelvis SRT (± ADT) but the advantages must be weighed against possible side effects [1083].

The optimal SRT dose has not been well defined. It should be at least 64 Gy to the prostatic fossa (± the base of the SVs, depending on the pathological stage after RP) [958, 1060, 1084]. In a systematic review, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that the treatment dose above 70 Gy should be administered at the lowest possible PSA level [1085]. The combination of pT stage, margin status and ISUP grade and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [950, 1086, 1087]. In a study on 894 node-negative PCa patients, doses ranging from 64 to > 74 Gy were assigned to twelve risk groups defined by their pre-SRT PSA classes < 0.1, 0.1–0.2, 0.2–0.4, and > 0.4 ng/mL and ISUP grade, < 1 vs. 2/3 vs. > 4 [1088]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [1070].

Two RCT’s were recently published (Table 6.3.5). Intensity-modulated radiation therapy plus IGRT was used in 57% of the patients in the SAKK-trial [958] and in all patients of the Chinese trial [1089]. No patient had a PSMA PET/CT before randomisation. The primary endpoint in both trials was ‘freedom from biochemical progression’, which was not significantly improved with higher doses. However, in the Chinese trial a subgroup analysis showed a significant improvement of this endpoint for patients with Gleason 8-10 tumours (79.7% vs. 55%, p = 0.049). In this trial, patients were treated with ART or SRT and the number of patients was relatively small (n = 144). At this time it seems difficult to draw final conclusions about the optimal total RT-dose and longer follow-up should be awaited.

Table 6.3.5: Randomized trials investigating dose escalation for SRT without ADT and without PET-CT

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
SAKK 09/10 trial, 2021 [958]	350	pT2a-3b R0 – R1 pN0 or cN0 PSA post-op undetectable (< 0.1 ng/mL) or persistent (> 0.1 ng/mL < 0.4 ng/mL)	64 Gy vs.70 Gy No ADT allowed VMAT + IGRT: 57% 3-D planning: 43%	6.2 yr.	Primary endpoint: FFBP	**6 yr. FFBP: 62% vs. 61%** **OS: no difference** **Late side effects:** **GI grade 2: 7.3% vs. 20%** **GI grade 3: 4.2% vs. 2.3%** p for ≥ grade 2/3: 0.009
Phase-III-Trial Qi X, *et al.*, 2020 [1089]	144 ART: 33% SRT: 67%	pT2-4 R0-R1 pN0 or cN0 Med. PSA pre-RT: 0.2 ng/mL	66 Gy vs. 72 Gy All patients VMAT + IGRT No ADT allowed High risk (pT3–4, GS: 8–10, PSA > 20 ng/mL): whole pelvis RT: 126 (87.5%)	49 mo.	Primary endpoint: FFBP	**4 yr. FFBP: 75.9% vs. 82.6%** (p > 0.05) **High risk (GS: 8–10): 55.7% vs. 79.7%** p < 0.049) **Late side effects:** **GI + GU grade 2** **p > 0.05** **No grade 3**

ADT = androgen deprivation therapy; ART = adjuvant radiotherapy; FFBP = freedom from biochemical failure; GI = gastro-intestinal; GU = genito-urinary; Gy: Gray; IGRT = image guided radiotherapy; mo = month; n = number of patients; PSA = prostate-specific antigen; RT = radiotherapy; SRT = y = year; vs. = versus; VMAT = volumetric arc radiation therapy.

Salvage RT is associated with toxicity. In one report on 464 SRT patients receiving median 66.6 (max. 72) Gy, acute grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late grade 3 reactions of the GI tract, but overall, severe GU tract toxicity was not observed. Late grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [1068].

In a RCT on dose escalation for SRT (n = 350), acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64 Gy and in 16.6% and 1.7%, respectively, with 70 Gy. Gastro-intestinal tract grades 2 and 3 toxicity occurred in 16.0% and 0.6%, respectively, with 64 Gy, and in 15.4% and 2.3%, respectively, with 70 Gy. Late effects have yet to be reported [1090, 1091]. Late grade 2 and 3 GI toxicity was significantly increased with higher doses but without significant differences in QoL. In this study, however, the rectal wall dose constraints were rather permissive and in 44% of the patients outdated 3-D-techniques were used [958].

With dose escalation over 72 Gy and/or up to a median of 76 Gy, the rate of severe side effects, especially GU symptoms, clearly increases, even with newer planning and treatment techniques [1092, 1093]. In particular, when compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02) but no effect on the relatively high level of GU toxicity was shown (5-year, 3D-CRT 15.8% vs. IMRT 16.8%) [1092]. However, in a RCT comparing 66 Gy and 72 Gy with all patients having IMRT plus IGRT (n = 144), no significant differences for GI and GU-toxicity was demonstrated [1089]. After a median salvage IMRT dose of 76 Gy however, the 5-year risk of grade 2–3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [1093]. Doses of at least 64 Gy and up to 72 Gy in patients without PET/CT can be recommended [1068, 1090].

6.3.5.1.2.2 Salvage RT with or without ADT (cTx CN0/1) with PET/CT

In a prospective multi-centre study of 323 patients with BCR, PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [463]. A prospective study

in a subgroup of 119 BCR patients with low PSA (< 0.5 ng/mL) reported a change in the intended treatment in 30.2% of patients [983]; however, no data exist on the impact on final outcome. Another prospective study in 272 patients with early biochemical recurrent PCa after RP showed that ^{68}Ga-PSMA-ligand PET/CT may tailor further therapy decisions (e.g., local vs. systemic treatment) at low PSA values (0.2–1 ng/mL) [985].

A single-centre study retrospectively assessed 164 men from a prospective database who underwent imaging with PSMA PET/CT for a rising PSA after RP with PSA levels < 0.5 ng/mL. In men with a negative PSMA PET/CT who received salvage RT, 85% (23 out of 27) demonstrated a treatment response compared to a further PSA increase in 65% of those not treated (22 out of 34). In the 36/99 men with disease confined to the prostate fossa on PSMA, 83% (29 out of 36) responded to salvage RT [1094]. Thus, PSMA PET/CT might stratify men into a group with high response (negative findings or recurrence confined to the prostate) and poor response (positive nodes or distant disease) to salvage RT. As there are no prospective phase III data (in particular not for PCa-specific survival or OS) these results have to be confirmed before a recommendation can be provided.

A single-centre open-label, phase II/III RCT (EMPIRE-1) evaluated the role of ^{18}F-fluciclovine-PET/CT compared with conventional imaging for salvage RT. Three hundred and sixty five patients with detectable PSA after RP but negative results on conventional imaging, were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT; patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow-up was 3.5 years. In adjusted analyses, the study group was significantly associated with event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1050].

6.3.5.1.2.3 Metastasis-directed therapy for rcN+ (with PET/CT)

Radiolabelled PSMA PET/CT is increasingly used as a diagnostic tool to assess metastatic disease burden in patients with BCR following prior definitive therapy. A review including 30 studies and 4,476 patients showed overall estimates of positivity in a restaging setting of 38% in pelvic LNs and 13% in extra-pelvic LN metastases [982]. The percentage positivity of PSMA PET/CT was proven to increase with higher PSA values, from 33% (95% CI: 16–51) for a PSA of < 0.2 ng/mL, to 45% (39–52), 59% (50–68), 75% (66–84), and 95% (92–97) for PSA subgroup values of 0.2–0.49, 0.5–0.99, 1.00–1.99, and > 2.00 ng/mL, respectively [982]. Results of this review demonstrated high sensitivity and specificity of ^{68}Ga-PSMA PET in advanced PCa with a per-lesion-analysed sensitivity and specificity of 75% and 99%, respectively.

In patients relapsing after a local treatment (including cN+ and highly selected M1 patients), a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. Metastasis-directed (MDT) therapy in PET/CT detected nodal oligo-recurrent PCa after RP was assessed in a large retrospective multi-institutional study (263 patients received MDT and 1,816 patients SOC as control group [matched 3:1]). Metastasis-targeting therapy consisted of salvage LN resection (n = 166) and stereotactic ablation RT (SABR) (n = 97). After a median follow-up of 70 months, the MDT-group showed significantly better CSS (5-year survival 98.6% vs. 95.7%, p < 0.01, respectively), however, these results should be viewed with caution as this was a retrospective study, the findings of which require further validation in prospective trials [1095].

Another retrospective study compared SABR with elective nodal irradiation (ENRT) in PET/CT-detected nodal oligo-recurrent PCa (n = 506 patients, 365 of which with N1 pelvic recurrence). With a median follow-up of 36 months, ENRT (n = 197) was associated with a significant reduction of nodal recurrences compared with SABR (n = 309) of 2% vs. 18%, respectively, but at the cost of higher side effects of ENRT [1096]. These results have to be confirmed in prospective trials before any recommendations can be made. In these situations SABR should be used in highly selected patients in prospective cohorts or clinical trials only. For MDT in M1-patients see Section 6.4.7.

A phase II trial assessed the biochemical response after ^{18}F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1097].

Phillips and colleagues reported outcomes of the phase II ORIOLE (Observation vs. Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer) clinical trial in patients with hormone-sensitive oligometastatic PCa randomised to receive SABR or observation alone [1098]. The primary outcome was the proportion of patients with disease progression at 6 months. Fifty-four patients were randomised and progression at 6 months occurred in 19% of patients receiving SABR and in 61% undergoing observation. In a *post-hoc* analysis, total consolidation of PSMA-positive disease decreased the risk of new lesions at 6 months (16% vs. 63%; p.= 0.0.006).

A review on new generation imaging modalities (whole-body MRI and PET with choline or fluciclovine or sodium fluoride or PSMA) for the detection of recurrent oligometastatic hormone-sensitive PCa showed that PSMA and choline PET can contribute to guiding MDT [1099]. However, such studies should still be considered as experimental as no data demonstrating the clinical significance of any outcomes are available. For MDT in M1-patients see Section 6.4.7.

6.3.5.1.3 Salvage lymph node dissection

The surgical management of (recurrent) nodal metastases in the pelvis has been the topic of several retrospective analyses [1100-1102] and a systematic review [1103]. The reported 5-year BCR-free survival rates ranged from 6% to 31%. Five-year OS was approximately 84% [1103]. Biochemical recurrence rates were found to be dependent on PSA at surgery and location and number of positive nodes [1104]. Addition of RT to the lymphatic template after salvage LN dissection may improve the BCR rate [1105]. In a multi-centre retrospective study long-term outcomes of salvage LN dissection were reported to be worse than previously described in studies with shorter follow-up [1106]. Biochemical recurrence-free survival at 10 years was 11%. Patients with a PSA response after salvage LN dissection and patients receiving ADT within 6 months from salvage LN dissection had a lower risk of death from PCa [1106]. High-level evidence for the oncological value of salvage LN dissection is still lacking [1103].

6.3.5.1.4 Comparison of adjuvant- and salvage radiotherapy

Section 6.2.5.4 is referred to for more details. Main findings are that after RP the vast majority of patients do not need ART which is supported by the results of 3 phase III RCTs comparing adjuvant RT and early salvage RT with a median follow-up of 5 years [953-957].

However, longer term (10-year) results and results of metastasis-free survival endpoints are needed before final conclusions can be drawn. Due to the small number of patients with adverse pathology (ISUP grade group 4–5 and pT3) included in these 3 trails (only approximately 20%) ART remains a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients') i.e. ISUP grade group 4–5 and pT3 with or without positive margins. This is supported by retrospective studies [957, 959].

6.3.5.2 Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or salvage local procedures. A systematic review and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage HIFU, salvage cryotherapy, SBRT, salvage LDR brachytherapy, and salvage HDR brachytherapy in the management of locally recurrent PCa after primary radical EBRT [1107]. The outcomes were BCR-free survival at 2 and 5 years. No significant differences with regards to recurrence-free survival (RFS) between these modalities was found. Five-year RFS ranged from 50% after cryotherapy to 60% after HDR brachytherapy and SBRT. The authors reported that severe GU toxicity exceeded 21% for HIFU and RP, whereas it ranged from 4.2% to 8.1% with re-irradiation. Differences in severe GI toxicity also appeared to favour re-irradiation, particularly HDR brachytherapy [1107]. Due to the methodological limitations of this review (the majority of the included studies were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes) the available evidence for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made. The following is an overview of the most important findings for each of these techniques.

6.3.5.2.1 Salvage radical prostatectomy

Salvage RP after RT is associated with a higher likelihood of adverse events (AEs) compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation [1108].

6.3.5.2.1.1 Oncological outcomes

In a systematic review of the literature, Chade, *et al*., showed that SRP provided 5- and 10-year BCR-free survival estimates ranging from 47–82% and from 28–53%, respectively. The 10-year CSS and OS rates ranged from 70–83% and from 54–89%, respectively. The pre-SRP PSA value and prostate biopsy ISUP grade were the strongest predictors of the presence of organ-confined disease, progression, and CSS [1109]. In a multi-centre analysis including 414 patients, 5-year BCR-free survival, CSS and OS were 56.7%, 97.7% and 92.1%, respectively [1110]. Pathological T stage ≥ T3b (OR: 2.348) and GS (up to OR 7.183 for GS > 8) were independent predictors for BCR (see Table 6.3.6).

Table 6.3.6: Oncological results of selected salvage radical prostatectomy case series

Study	n	Median FU (mo)	Pathologic Organ-confined (%)	PSM (%)	Lymph-node involvement (%)	BCR-free probability (%)	CSS (%)	Time probability
Chade, *et al*. 2011 [1111]	404	55	55	25	16	37	83	10 yr.
Mandel, *et al*. 2016 [1112]	55	36	50	27	22	49	89	5 yr.
Ogaya-Pinies, *et al*. 2018 [1113]	96	14	50	17	8	85*	-	14 mo.
Marra, *et al*. 2021 [1110]	414	36	46	30	16	57	98	5 yr.

**Percentage of patients without BCR.*
BCR = biochemical recurrence; CSS = cancer-specific survival; FU = follow-up; mo = months; n = number of patients; PSM = positive surgical margin.

6.3.5.2.1.2 Morbidity
Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [1114]. In more recent series, these complications appear to be less common [1108, 1109, 1112].

Functional outcomes are also worse compared to primary surgery, with urinary incontinence ranging from 21% to 90% and ED in nearly all patients (see Table 6.3.7) [1109, 1112].

Table 6.3.7: Peri-operative morbidity in selected salvage radical prostatectomy case series

Study	n	Rectal injury (%)	Anastomotic stricture (%)	Clavien 3-5 (%)	Blood loss, mL, mean, range
Ward, *et al*. 2005 [1115]	138	5	22	-	-
Sanderson, *et al*. 2006 [1116]	51	2	41	6	-
Gotto, *et al*. 2010 [1114]	98	9	41	25	-
Gontero, *et al*. 2019 [1108]	395	1.6	25	3.6	10.1

n = number of patients.

6.3.5.2.1.3 Summary of salvage radical prostatectomy
In general, SRP should be considered only in patients with low co-morbidity, a life expectancy of at least 10 years, a pre-SRP PSA < 10 ng/mL and initial biopsy ISUP grade ≤ 2/3, no LN involvement or evidence of distant metastatic disease pre-SRP, and those whose initial clinical staging was T1 or T2 [1109].

A meta-analysis and systematic review of local salvage therapies after RT for PCa has suggested that re-irradiation with SBRT, HDR brachytherapy or LDR brachytherapy appears to result in less severe GU toxicity than RP, and re-irradiation with HDR brachytherapy in less severe GI toxicity than RP [1107].

6.3.5.2.2 Salvage cryoablation of the prostate
6.3.5.2.2.1 Oncological outcomes
Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to salvage RP, as it has a potentially lower risk of morbidity and equal efficacy.

In a systematic review a total of 32 studies assessed SCAP, recruiting a total of 5,513 patients. The overwhelming majority of patients (93%) received whole-gland SCAP. The adjusted pooled analysis for 2-year BCR-free survival for SCAP was 67.49% (95% CI: 61.68–72.81%), and for 5-year BCR-free survival was 50.25% (95% CI: 44.10–56.40%). However, the certainty of the evidence was low. Table 6.3.8 summarises the results of a selection of the largest series on SCAP to date in relation to oncological outcomes (BCR only) [1107].

Table 6.3.8: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Ginsburg, *et al*. 2017 [1117]	898	19.0	5	71.3%	Phoenix criteria
Spiess, *et al*. 2010 [1118]	450	40.8	3.4	39.6%	PSA > 0.5 ng/mL
Li, *et al*. 2015 [1119]	486	18.2	5	63.8%	Phoenix criteria
Kovac, *et al*. 2016 [1120]	486	18.2	5	75.5% (nadir PSA < 0.4 ng/mL); 22.1% (nadir PSA ≥ 0.4 ng/mL)	Phoenix criteria
Ahmad, *et al*. 2013 [1121]	283	23.9	3	67.0% (nadir PSA ≤ 1 ng/mL); 14.0% (nadir PSA > 1 ng/mL)	Phoenix criteria
Pisters, *et al*. 2008 [1122]	279	21.6	5	58.9% (ASTRO) 54.5% (Phoenix)	ASTRO and Phoenix criteria

ASTRO = American Society for Therapeutic Radiology and Oncology; BCR = biochemical recurrence; FU = follow-up; mo. = months; n = number of patients; PSA = prostate-specific antigen; yr. = year.

6.3.5.2.2.2 Morbidity

The main adverse effects and complications relating to SCAP include urinary incontinence, urinary retention due to bladder outflow obstruction, recto-urethral fistula, and ED. A systematic review and meta-analysis showed an adjusted pooled analysis for severe SCAP-related GU toxicity of 15.44% (95% CI: 10.15–21.54%) [1107]. As before, the certainty of the evidence was low. Table 6.3.9 summarises the results of a selection of the largest series on SCAP to date in relation to GU outcomes.

Table 6.3.9: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage cryoablation case series, including at least 100 patients

Study	n	Time point of outcome measurement (mo)	Incontinence (%)	Obstruction/ Retention (%)	Rectourethral fistula (%)	ED (%)
Li, *et al*. 2015 [1119]	486	12	33.3	21.7	4.7	71.3
Ahmad, *et al*. 2013 [1121]	283	12	12.0	8.1	1.8	83.0
Pisters, *et al*. 2008 [1122]	279	12	4.4	3.2	1.2	NA
Cespedes, *et al*. 1997 [1123]	143	Median 27.0	28.0	14.0	NA	NA
Chin, *et al*. 2001 [1124]	118	Median 18.6	6.7	NA	3.3	NA

ED = erectile dysfunction; mo = months; n = number of patients.

6.3.5.2.2.3 Summary of salvage cryoablation of the prostate

In general, the evidence base relating to the use of SCAP is poor, with significant uncertainties relating to long-term oncological outcomes, and SCAP appears to be associated with significant morbidity. Consequently, SCAP should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study.

6.3.5.2.3 Salvage re-irradiation

6.3.5.2.3.1 Salvage brachytherapy for radiotherapy failure

Carefully selected patients with a good PS, primary localised PCa, good urinary function and histologically proven local recurrence are candidates for salvage brachytherapy using either HDR- or LDR.

In a systematic review a total of 16 studies (4 prospective) and 32 studies (2 prospective) assessed salvage HDR and LDR brachytherapy, respectively, with the majority (> 85%) receiving whole-gland brachytherapy rather than focal treatment [1107]. The adjusted pooled analysis for 2-year BCR-free survival for HDR was 77% (95% CI: 70–83%) and for LDR was 81% (95% CI:74–86%). The 5-year BCR-free survival for

HDR was 60% (95% CI: 52–67%) and for LDR was 56% (95% CI: 48–63%). As noted above, brachytherapy techniques are associated with lower rates of severe GU toxicity when compared to RP or HIFU, at 8% for HDR (95% CI: 5.1–11%) and 8.1% for LDR (95% CI: 4.3–13%). Rates of severe GI toxicity are reported to be very low at 0% for HDR (95% CI: 0–0.2%) and 1.5% for LDR (95% CI: 0.2–3.4%). High-dose-rate or LDR brachytherapy are effective treatment options with an acceptable toxicity profile. However, the published series are small and likely under-report toxicity. Consequently, this treatment should be offered in experienced centres ideally within randomised clinical trials or prospective registry studies (see Table 6.3.10).

Table 6.3.10: Treatment-related toxicity and BCR-free probablity in selected salvage brachytherapy studies including at least 100 patients.

Study	Study design	n and BT type	Median FU (mo)	Treatment toxicity	BCR-free probability
Lopez, *et al*. 2019 [1125]	multi-centre retrospective	75 HDR 44 LDR	52	23.5% late G3+ GU	5 yr 71% (95% CI: 65.9-75.9%)
Crook, *et al*. 2019 [1126]	multi-centre prospective	100 LDR	54	14% late G3 combined GI/GU	n.r.
Smith, *et al*. 2020 [1127]	single-centre retrospective	108 LDR	76	15.7%/2.8% late G3 GU/GI	5 yr. 63.1% 10 yr. 52%
Lyczek, *et al*. 2009 [1128]	single-centre retrospective	115 HDR	n.r.	12.2%/0.9% late G3+ GU/GI	60% at 40 mo.

BT = brachytherapy; CI; confidence interval; G = grade; GI = gastro-intestinal; GU = genito-urinary; HDR = high-dose rate; LDR = low-dose rate; mo = months; n = number of patients; n.r. = not reported; yr = year.

6.3.5.2.3.2 Salvage stereotactic ablative body radiotherapy for radiotherapy failure

6.3.5.2.3.2.1 Oncological outcomes and morbidity

Stereotactic ablative body radiotherapy (CyberKnife® or linac-based treatment) is a potentially viable new option to treat local recurrence after RT. Carefully selected patients with good IPSS-score, without obstruction, good PS and histologically proven localised local recurrence are potential candidates for SABR. In a meta-analysis and systematic review five mostly retrospective studies including 206 patients were treated with CyberKnife® or linac-based treatment showing 2-year RFS estimates (61.6%, 95% CI: 52.6–69.9%) [1107]. In a retrospective multi-centre study (n = 100) the median pre-salvage PSA was 4.3 ng/mL with 34% of patients having received ADT for twelve months (median). All recurrences were biopsy proven. Patients were treated with the CyberKnife® with a single dose of 6 Gy in six daily fractions (total dose 36 Gy). With a median follow-up of 30 months the estimated 3-year second BCR-free survival was 55% [1129].

In a smaller retrospective series including 50 men with histologically proven local recurrence with a median pre-salvage PSA of 3.9 ng/mL only 15% had received additional ADT. The estimated 5-year second BCR-free survival was 60% (median follow-up of 44 months) which is an outcome comparable to series treating patients with RP, HIFU or brachytherapy [1130]. Table 6.3.11 summarises the results of the two larger SABR series addressing oncological outcomes and morbidity.

Table 6.3.11: Treatment-related toxicity and BCR-free survival in selected SABR studies including at least 50 patients

Author	Study design	n and RT-type	Median FU (mo)	Fractionation (SD/TD)	ADT	Treatment toxicity	BCR-free survival
Fuller, *et al.* 2020 [1130]	single-centre retrospective	50 Cyber Knife	44	SD 6.8 Gy TD 34 Gy	7/50	5 yr: 8% late G3+ GU	5 yr. 60%
Pasquier, *et al.* 2020 [1129]	multi-centre retrospective	100 Cyber Knife	30	SD 6 Gy TD 36 Gy	34/100 median 12 mo.	3 yr. grade 2+ GU 20.8% GI 1%	3 yr. 55%

BCR = biochemical recurrence-free; FU = follow-up; mo = months; n = number of patients; RT-type = type of radiotherapy; SD = single dose; TD = total dose; yr = year.

6.3.5.2.3.2.2 Morbidity

In a retrospective single-centre study with 50 consecutive patients chronic significant toxicity was only seen for the GU domain with 5-year grade 2+ and grade 3+ GU rates of 17% and 8%, respectively. No GI toxicity > grade 1 was seen. Of note, of the fifteen patients who were sexually potent pre-salvage SBRT, twelve

subsequently lost potency [1130]. In a retrospective French (GETUG) multi-centre series (n = 100) the 3-year late grade 2+ GU and GI toxicity was 20.8% (95% CI: 13–29%) and 1% (95% CI: 0.1–5.1%), respectively [1129].

6.3.5.2.3.2.3 Summary of salvage stereotactic ablative body radiotherapy

Despite the encouraging results so far the number of patients treated with SABR is relatively limited. In view of the rates of higher grade 2+ GU side effects, SABR should only be offered to selected patients, in experienced centres as part of a clinical trial or well-designed prospective study.

6.3.5.2.4 Salvage high-intensity focused ultrasound

6.3.5.2.4.1 Oncological outcomes

Salvage HIFU has emerged as an alternative thermal ablation option for radiation-recurrent PCa. Being relatively newer than SCAP the data for salvage HIFU are even more limited. A systematic review and meta-analysis included 20 studies (n = 1,783) assessing salvage HIFU [1107]. The overwhelming majority of patients (86%) received whole-gland salvage HIFU. The adjusted pooled analysis for 2-year BCR-free survival for salvage HIFU was 54.14% (95% CI: 47.77–60.38%) and for 5-year BCR-free survival 52.72% (95% CI: 42.66–62.56%). However, the certainty of the evidence was low. Table 6.3.12 summarises the results of a selection of the largest series on salvage HIFU to date in relation to oncological outcomes (BCR only).

Table 6.3.12: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Crouzet, *et al*. 2017 [1131]	418	39.6	5	49.0%	Phoenix criteria
Murat, *et al*. 2009 [1132]	167	Mean 18.1	3	25.0% (high-risk) 53.0% (low-risk)*	Phoenix criteria or positive biopsy or initiation of post-HIFU salvage therapy
Kanthabalan, *et al*. 2017 [1133]	150	35.0	3	48.0%	Phoenix criteria
Jones, *et al*. 2018 [1134]	100	12.0	1	50.0%	Nadir PSA > 0.5 ng/mL or positive biopsy

**Results stratified by pre-EBRT D'Amico risk groups*

BCR = biochemical recurrence; FU = follow-up; mo = months; n = number of patients; yr = year.

6.3.5.2.4.2 Morbidity

The main adverse effects and complications relating to salvage HIFU include urinary incontinence, urinary retention due to bladder outflow obstruction, rectourethral fistula and ED. The systematic review and meta-analysis showed an adjusted pooled analysis for severe GU toxicity for salvage HIFU of 22.66% (95% CI: 16.98–28.85%) [1107]. The certainty of the evidence was low. Table 6.3.13 summarises the results of a selection of the largest series on salvage HIFU to date in relation to GU outcomes.

Table 6.3.13: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage HIFU case series, including at least 100 patients

Study	n	Time point of outcome measurement (yr)	Incontinence* (%)	Obstruction/ retention (%)	Rectourethral fistula (%)	ED (%)
Crouzet, *et al*. 2017 [1131]	418	Median 39.6	42.3	18.0	2.3	n.r.
Murat, *et al*. 2009 [1132]	167	Median 18.1	49.5	7.8	3.0	n.r.
Kanthabalan, *et al*. 2017 [1133]	150	24	12.5	8.0	2.0	41.7

Jones, *et al*. 2018 [1134]	100	12	42.0	49.0	5.0	74.0

**Incontinence was heterogeneously defined; figures represent at least 1 pad usage.*
ED = erectile dysfunction; n.r. = not reported; n = number of patients.

6.3.5.2.4.3 Summary of salvage high-intensity focused ultrasound
There is a lack of high-certainty data which prohibits any recommendations regarding the indications for salvage HIFU in routine clinical practice. There is also a risk of significant morbidity associated with its use in the salvage setting. Consequently, salvage HIFU should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study.

6.3.6 Hormonal therapy for relapsing patients

The Panel conducted a systematic review including studies published from 2000 onwards [1135]. Conflicting results were found on the clinical effectiveness of HT after previous curative therapy of the primary tumour. Some studies reported a favourable effect of HT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early HT group) [1136]. Other studies did not find any differences between early vs. delayed, or no, HT. One study found an unfavourable effect of HT [1137]. This may be the result of selecting clinically unfavourable cases for (early) HT and more intensive diagnostic workup and follow-up in these patients.

The studied population is highly heterogeneous regarding their tumour biology and therefore clinical course. Predictive factors for poor outcomes were; CRPC, distant metastases, CSS, OS, short PSA-DT, high ISUP grade, high PSA, increased age and co-morbidities. In some studies, such as the Boorjian, *et al*., study [1065], high-risk patients, mainly defined by a high ISUP grade and a short PSA-DT (most often less than 6 months) seem to benefit most from (early) HT, especially men with a long life expectancy.

No data were found on the effectiveness of different types of HT, although it is unlikely that this will have a significant impact on survival outcomes in this setting. Non-steroidal anti-androgens have been claimed to be inferior compared to castration, but this difference was not seen in M0 patients [1064]. One of the included RCTs suggested that intermittent HT is not inferior to continuous HT in terms of OS and CSS [1138]. A small advantage was found in some QoL domains but not overall QoL outcomes. An important limitation of this RCT is the lack of any stratifying criteria such as PSA-DT or initial risk factors. Based on the lack of definitive efficacy and the undoubtedly associated significant side effects, patients with recurrence after primary curative therapy should not receive standard HT since only a minority of them will progress to metastases or PCa-related death. The objective of HT should be to improve OS, postpone distant metastases, and improve QoL. Biochemical response to only HT holds no clinical benefit for a patient. For older patients and those with co-morbidities the side effects of HT may even decrease life expectancy; in particular cardiovascular risk factors need to be considered [1139, 1140]. Early HT should be reserved for those at the highest risk of disease progression defined mainly by a short PSA-DT at relapse (< 6–12 months) or a high initial ISUP grade (> 2/3) and a long life expectancy.

6.3.7 Observation

In unselected relapsing patients the median actuarial time to the development of metastasis will be 8 years and the median time from metastasis to death will be a further 5 years [937]. For patients with EAU Low-Risk BCR features (see Section 6.3.3), unfit patients with a life expectancy of less than 10 years or patients unwilling to undergo salvage treatment, active follow-up may represent a viable option.

6.3.8 Guidelines for second-line therapy after treatment with curative intent

Local salvage treatment	Strength rating
Recommendations for biochemical recurrence (BCR) after radical prostatectomy	
Offer monitoring, including prostate-specific antigen (PSA), to EAU Low-Risk BCR patients.	Weak
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive PSA rises.	Strong
A negative positron emission tomography/computed tomography (PET/CT) scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with BCR.	Weak

Recommendations for BCR after radiotherapy	
Offer monitoring, including PSA to EAU Low-Risk BCR patients.	Weak
Only offer salvage radical prostatectomy (RP), brachytherapy, high-intensity focused ultrasound, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
Recommendations for systemic salvage treatment	
Do not offer androgen deprivation therapy to M0 patients with a PSA-doubling time > 12 months.	Strong

6.4 Treatment: Metastatic prostate cancer

6.4.1 Introduction

All prospective data available rely on the definition of M1 disease based on CT scan and bone scan. The influence on treatment and outcome of newer, more sensitive, imaging has not been assessed yet.

6.4.2 Prognostic factors

Median survival of patients with newly diagnosed metastases is approximately 42 months with ADT alone, however, it is highly variable since the M1 population is heterogeneous [1141]. Several prognostic factors for survival have been suggested including the number and location of bone metastases, presence of visceral metastases, ISUP grade, PS status and initial PSA alkaline phosphatase, but only few have been validated [1142-1145].

'Volume' of disease as a potential predictor was introduced by CHAARTED (Chemo-hormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) [1145-1147] and has been shown to be predictive in a powered subgroup analysis for benefit of addition of prostate RT ADT [1148].

'Metachronous' metastatic disease vs. synchronous (or *de novo*) metastatic disease has also been shown to have a better prognosis [1149].

Based on a large SWOG 9346 cohort, the PSA level after 7 months of ADT was used to create 3 prognostic groups (see Table 6.4.2) [1150]. A PSA ≤ 0.2 ng/mL at 7 months has been confirmed as a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study independent of the addition of docetaxel [1151].

Table 6.4.1 Definition of high- and low-volume and risk in CHAARTED [1145-1147] **and LATITIDE** [812]

	High	Low
CHAARTED (volume)	≥ 4 Bone metastasis including ≥ 1 outside vertebral column or pelvis **OR** Visceral metastasis*	Not high
LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP grade 4	Not high

**Lymph nodes are not considered as visceral metastases.*

Table 6.4.2: Prognostic factors based on the SWOG 9346 study [1150]

PSA after 7 months of castration	Median survival on ADT monotherapy
< 0.2 ng/mL	75 months
0.2 ≤ 4 ng/mL	44 months
> 4 ng/mL	13 months

6.4.3 First-line hormonal treatment

Primary ADT has been the SOC for over 50 years [775]. There is no high-level evidence in favour of a specific type of ADT for oncological outcomes, neither for orchiectomy nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist, therefore patients with impending spinal cord compression or other potential impending complications from the cancer should be treated with either a bilateral orchidectomy or LHRH antagonists as the preferred options.

There is a suggestion in some studies that cardiovascular side effects are less frequent in patients

treated with LHRH antagonists vs. in patients treated with LHRH agonists [795, 1152, 1153]; therefore patients with pre-existing cardiovascular disease or other cardio-vascular risk factors might be considered to be treated with antagonists if a chemical castration is chosen.

6.4.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to AEs [1154]. The evidence quality of the studies included in this review was rated as moderate.

6.4.3.2 Intermittent versus continuous androgen deprivation therapy

Three independent reviews [1155-1157] and two meta-analyses [1158, 1159] looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All of these reviews included 8 RCTs of which only 3 were conducted in patients with exclusively M1 disease. The 5 remaining trials included different patient groups, mainly locally-advanced and metastatic patients relapsing.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [1160]. Out of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights that, at best, only 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: the actual upper limit was above the pre-specified 90% upper limit of 1.2 (HR: 1.1, CI: 0.99–1.23), the pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study inferior survival with IAD cannot be completely ruled out.

Other trials did not show any survival difference with an overall HR for OS of 1.02 (0.94–1.11) [1155]. These reviews and the meta-analyses came to the conclusion that a difference in OS or CSS between IAD and continuous ADT is unlikely. A review of the available phase III trials highlighted the limitations of most trials and suggested a cautious interpretation of the non-inferiority results [1161]. None of the trials that addressed IAD vs. continuous ADT in M1 patients showed a survival benefit but there was a constant trend towards improved OS and PFS with continuous ADT. However, most of these trials were non-inferiority trials. In some cohorts the negative impact on sexual function was less pronounced with IAD. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side effects such as hot flushes [1162, 1163].

6.4.3.3 Early versus deferred androgen deprivation therapy

There is an increasing body of evidence that early start of hormonal treatment also for the newer generation hormonal treatments is beneficial. Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease despite lack of randomised phase III data in this specific setting and specifically not with the combination therapies that are standard nowadays.

A 2002 Cochrane review included four RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [1164]. These studies were conducted in the pre-PSA era and included patients with advanced metastatic or non-metastatic PCa who received immediate vs. deferred ADT [1164]. No improvement in PCa CSS was observed, although immediate ADT significantly reduced disease progression. The Cochrane analysis was updated in 2019 and concluded that early ADT probably extends time to death of any cause and time to death from PCa [1165]. Since the analysis included only a very limited number of M1 patients who were not evaluated separately, the benefit of early ADT in this setting remains unproven. All of the trials testing the combination therapies in the metastatic hormone-sensitive setting also included asymptomatic patients.

The only candidates with metastasised disease who may possibly be considered for deferred treatment are asymptomatic patients with a strong wish to avoid treatment-related side effects. The risk of developing symptoms, and even dying from PCa, without receiving the benefit from hormone treatment with deferred treatment has been highlighted [873, 885], but in the era before next generation imaging was used.

Patients with deferred treatment for advanced PCa must be amenable to close follow-up. Another potential exception are patients with recurrent oligometastatic disease who have a strong wish to postpone the start of ADT (see Section 6.4.7).

6.4.4 ***Combination therapies***

All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.4.4.1 'Complete' androgen blockade with older generation NSAA

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [1166]. However, results with other anti-androgens or castration modalities have differed and

systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [1167, 1168] beyond 5 years of survival [1169] but this minimal advantage in a small subset of patients must be balanced against the increased side effects associated with long-term use of NSAAs. In addition, the newer combination therapies (see Tables 6.4.3, 6.4.4, 6.4.5) are more effective as shown specifically for enzalutamide vs. NSAA in a phase III trial [1170], therefore combination with NSAAs should only be considered if the other combination therapies are not available.

6.4.4.2 Androgen deprivation combined with other agents

6.4.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [881, 1145, 1171]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within 3 months of ADT initiation). The primary objective in all three studies was to assess OS. The key findings are summarised in Table 6.4.3.

Table 6.4.3: Key findings - Hormonal treatment combined with chemotherapy

	STAMPEDE [881, 1172]		**GETUG-AFU 15** [1171]		**CHAARTED** [1145,1146]	
	ADT	ADT + Docetaxel + P	ADT	ADT + Docetaxel	ADT	ADT + Docetaxel
N	1,184	592	193	192	393	397
Newly diagnosed M+	58%	59%	75%	67%	73%	73%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL, or nodal or metastatic relapse		Metastatic disease Karnofsky score ≥ 70%		Metastatic disease ECOG PS 0, 1 or 2	
Primary objective	OS		OS		OS	
Median follow up (mo)	43; 78.2 (update M1)		50		54 (update)	
HR (95% CI)	0.78 (0.66-0.93)		1.01 (0.75-1.36)		0.72 (0.59-0.89)	
M1 only						
N	1,086		-		-	
HR (95% CI)	0.81 (0.69-0.95)		-		-	

ADT = androgen deprivation therapy; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ISUP = International Society for Urological Pathology; mo = month; n = number of patients; OS = overall survival; P = prednisone; PSA-DT = prostate-specific antigen-doubling time.

In the GETUG 15 trial, all patients had M1 PCa, either *de novo* or after a primary treatment [1171]. They were stratified based on previous treatment and Glass risk factors [1142]. In the CHAARTED trial the same inclusion criteria applied, and patients were stratified according to disease volume (see Table 6.4.1) [1145].

STAMPEDE is a multi-arm multi-stage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1 or N1 or having two of the following 3 criteria: T3/4, PSA ≥ 40 ng/mL or ISUP grade 4–5. Also relapsed patients after local treatment were included if they met one of the following criteria: PSA ≥ 4 ng/mL with a PSA-DT < 6 months or a PSA ≥ 20 ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [881]. In all 3 trials toxicity was mainly haematological with around 12–15% grade 3–4 neutropenia, and 6–12% grade 3–4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on

available guidelines [1173, 1174].

Based on these data, upfront docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [1174]. Docetaxel is used at the standard dose of 75 mg/sqm combined with steroids as pre-medication. Continuous oral corticosteroid therapy is not mandatory.

In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT is most evident in men with *de novo* metastatic high-volume disease [1146, 1147], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [1172]. The effects were less apparent in men who had prior local treatment although the numbers were small and the event rates lower. A systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to SOC improved survival [1174]. The HR of 0.77 (95% CI: 0.68–0.87, $p < 0.0001$) translates into an absolute improvement in 4-year survival of 9% (95% CI: 5–14). Docetaxel in addition to SOC also improves failure-free survival, with a HR of 0.64 (0.58–0.70, $p < 0.0001$) translating into a reduction in absolute 4-year failure rates of 16% (95% CI: 12–19).

6.4.4.2.2 Combination with the new hormonal treatments (abiraterone, apalutamide, enzalutamide)

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC was studied [40, 812, 1175]. The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [812]. The HR in STAMPEDE was very similar with 0.63 (0.52–0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [40]. While only high-risk patients were included in the LATITUDE trial a *post-hoc* analysis from STAMPEDE showed the same benefit whatever the risk or the volume stratification [1176].

All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were positive and in favour of the combination. The key findings are summarised in Table 6.4.4. No difference in treatment-related deaths was observed with the combination of ADT plus AAP compared to ADT monotherapy (HR: 1.37 [0.82–2.29]). However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%). Based on these data upfront AAP combined with ADT should be considered as a standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug (see Table 6.4.4) [1175].

In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with mHSPC was tested [810, 811, 1170]. In ARCHES the primary endpoint was radiographic PFS (rPFS). Radiographic PFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3–0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT improved OS with a HR of 0.67 (0.52–0.86). Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had low-volume disease [811]. In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. Radiographic PFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39–0.6); OS at 24 months was improved for the combination with a HR of 0.67 (0.51–0.89). In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [810].

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients treated had *de novo* metastatic disease and the evidence is most compelling in this situation. In the trials with the new AR antagonists, a proportion of patients had metachronous disease (see Table 6.4.5); therefore, a combination should also be considered for men progressing after radical local therapy. Lastly, whether the addition of a new AR antagonist plus docetaxel adds further OS benefit is currently unclear. Longer follow-up data are needed before a definitive conclusion is possible. At the moment, since toxicity clearly increases, AR antagonists plus docetaxel should not be given outside of clinical trials.

The addition of abiraterone to ADT and docetaxel has been reported to have a benefit in rPFS and in OS in the PEACE-1 trial [1176b]. Formal recommendation will be considered following publication of the data.

Table 6.4.4: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [40]		**LATITUDE** [812]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
N	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT - newly diagnosed M1 or N+ situations - locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40 ng/mL) - relapsing locally treated disease with a PSA > 4 ng/mL and a PSA-DT < 6 mo. or PSA > 20 ng/mL or nodal or metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: ISUP grade ≥ 4, ≥ 3 bone lesions, measurable visceral metastasis	
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	40		30.4	
3-yr. OS	**83% (ADT + AA + P)** **76% (ADT)**		**66% (ADT + AA + P)** **49% (ADT + placebo)**	
HR (95% CI)	0.63 (0.52 - 0.76)		0.62 (0.51-0.76)	
M1 only				
N	1,002		1,199	
3-yr. OS	NA		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.61 (0.49-0.75)		0.62 (0.51-0.76)	
HR	FFS (biological, radiological, clinical or death): 0.29 (0.25-0.34)		Radiographic PFS: 0.49 (0.39-0.53)	

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo = month; n = number of patients; NA = not available; OS = overall survival; P = prednisone; PFS = progression-free survival; PSA = prostate-specific antigen; yr. = year.

Table 6.4.5 Results from the ENZAMET and TITAN studies

	ENZAMET [1170]		**TITAN** [810]	
	ADT+ older antagonist +/-docetaxel (SOC)	ADT + enzalutamide +/-docetaxel	ADT + placebo	ADT + apalutamide
N	562	563	527	525
Newly diagnosed M+	72.1%	72.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS Radiographic PFS	
Median follow up (mo)	34		30.4	
3-yr. OS	3-yr survival: 80% (ADT + enzalutamide) 72% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.67 (0.52-0.86)		0.67 (0.51-0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo = month; n = number of patients; OS = overall survival; SOC = standard of care; PFS = progression-free survival; yr = year.

6.4.5 *Treatment selection and patient selection*

An ADT-based combination therapy is the SOC for patients with newly diagnosed mHSPC. There are no head-to-head data comparing 6 cycles of docetaxel and the continuous use of AAP or of apalutamide or of enzalutamide in newly diagnosed mHSPC. However, for a period, patients in STAMPEDE were randomised to either the addition of abiraterone or docetaxel to SOC. Data from the two experimental arms has been extracted although this was not pre-specified in the protocol and therefore the data were not powered for this comparison. The survival advantage for both drugs appeared similar [1177], patients receiving AAP plus SOC reported clinically meaningful higher global-QoL scores throughout the first two years compared to patients receiving docetaxel but statistical significance was not reached [1178]. A meta-analysis also found no significant OS benefit for either drug [1179]. Limitations of network meta-analyses include variable patient populations with different treatment benefits and follow-up periods. In the STOPCAP systematic review and meta-analysis, AAP was found to have the highest probability of being the most effective treatment [1180]. Both modalities have different and agent-specific side effects and require strict monitoring of side effects during treatment. Therefore, the choice will most likely be driven by patient preference, the specific side effects, fitness for docetaxel, availability and cost.

There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the combination therapies has been clearly proven to be superior over another [1181, 1182]. As a consequence, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on non-cancer co-morbidities).

6.4.6 *Treatment of the primary tumour in newly diagnosed metastatic disease*

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [1183]. The STAMPEDE trial evaluated 2,061 men with mCSPC who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1148]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved, and patients categorised as low- or high volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT and it must be highlighted that this benefit was obtained without an increased dose. The doses and template used in STAMPEDE should be considered (55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6-weekly fractions of 6 Gy or a biological equivalent total dose of 72 Gy). Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel and no patients had additional AAP, so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment as results of ongoing trials are awaited.

In a systematic review and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04, p = 0.195) [1184]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases.

6.4.7 *Metastasis-directed therapy in M1-patients*

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There are two randomised phase II trials testing metastasis-directed therapy (MDT) using surgery ± SABR vs. surveillance [1185] or SABR vs. surveillance in men with oligo-recurrent PCa [1098]. Oligo-recurrence was defined as ≤ 3 lesions on choline-PET/CT only [1185] or conventional imaging with MRI/CT and/or bone scan [1098]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1185]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1185]. The primary endpoint in the ORIOLE trial was progression after 6 months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1098]. Currently there is no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as experimental until the results of the ongoing RCT are available [1186, 1187].

6.4.8 *Guidelines for the first-line treatment of metastatic disease*

All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy (RT) (using the doses and template from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

6.5 Treatment: Castration-resistant PCa (CRPC)

6.5.1 *Definition of CRPC*

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL
   or
b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [1188]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

6.5.2 *Management of mCRPC - general aspects*

Selection of treatment for mCRPC is multifactorial and in general dependent on:

- previous treatment for mHSPC and for non-mHSPC;
- previous treatment for mCRPC;
- quality of response and pace of progression on previous treatment;
- known cross resistance between androgen receptor targeted agents (ARTA);
- co-medication and known drug interactions (see approved summary of product characteristics);
- known genetic alterations and microsatellite instability–high (MSI-H)/mismatch repair–deficient (*dMMR*) status;
- known histological variants and DNA repair deficiency (consider platinum or targeted therapy like PARPi;
- local approval status of drugs and reimbursement situation;
- available clinical trials;
- The patient and his co-morbidities.

6.5.2.1 Molecular diagnostics

All metastatic patients should be offered somatic genomic testing for homologous repair and *MMR* defects, preferably on metastatic carcinoma tissue but testing on primary tumour may also be performed. Alternatively, but still less common, genetic testing on circulating tumour DNA (ctDNA) is an option and has been used in some trials. One test, the FoundationOne® Liquid CDx, has been FDA approved [1189]. Defective *MMR* assessment can be performed by IHC for *MMR* proteins (*MSH2, MSH6, MLH1* and *PMS2*) and/or by next-generation sequencing (NGS) assays [1190]. Germline testing for *BRCA1/2, ATM* and *MMR* is recommended for high-risk and particularly for metastatic PCa if clinically indicated.

Molecular diagnostics should be performed by a certified (accredited) institution using a standard NGS multiplication procedure (minimum depth of coverage of 200 X). The genes and respective exons should be listed; not only DNA for mutations but RNA needs to be examined for fusions and protein expression to obtain all clinically relevant information. A critical asset is the decision support helping to rate the mutations according to their clinical relevance [1191, 1192].

Level 1 evidence for the use of PARP-inhibitors has been reported [1193-1195]. Microsatellite instability (MSI)-high (or *MMR* deficiency) is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA and could be a valuable additional treatment option [1196, 1197].

Germline molecular testing is discussed in Section 5.1.3 - Genetic testing for inherited PCa. Recommendations for germline testing are provided in Section 5.1.4.

*6.5.3 **Treatment decisions and sequence of available options***

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone, enzalutamide, cabazitaxel, olaparib and radium-223. In general, sequencing of ARTAs like abiraterone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARTA was short (≤ 12 months) and high-risk features of rapid progression are present (see detailed discussion in Section 6.5.8.2) [1198, 1199].

The use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence is recommended and should be applied early enough when the patient is still fit for chemotherapy. This is supported by high-level evidence [1198].

*6.5.4 **Non-metastatic CRPC***

Frequent PSA testing in men treated with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases within two years, detected by conventional imaging [207].

In men with CRPC and no detectable clinical metastases using bone scan and CT-scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone metastasis-free survival and OS [207, 1200]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2 ng/mL and if this was negative, it should be repeated when the PSA reached 5 ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1201]. Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA PET/CT or whole-body MRI, more patients are diagnosed with early mCRPC [1202]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

Three large phase III RCTs, PROSPER [1203], SPARTAN [1204] and ARAMIS [1205], evaluated metastasis-free survival as the primary endpoint in patients with nmCRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide vs. placebo (ARAMIS), respectively (see Table 6.5.1). The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ 10 months were included. Patient characteristics in trials revealed that about two-thirds of participants had a PSA-DT of < 6 months. All trials showed a significant metastasis-free survival benefit. All three trials showed a survival benefit after a follow-up of more than 30 months. In view of the long-term treatment with these AR targeting agents in asymptomatic patients, potential AEs need to be taken into consideration and the patient informed accordingly.

Table 6.5.1: Randomised phase III controlled trials – nmCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ARAMIS 2019, 2020 [1205, 1206]	ADT + darolutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**59% reduction of distant progression or death** **Median MFS: darolutamide 40.4 vs placebo 18.4 mo;** **31% reduction in risk of death** HR = 0.69 (95% CI: 0.53–0.88) p = 0.003
PROSPER 2018, 2020 [1203, 1207]	ADT + enzalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**71% reduction of distant progression or death** **Median MFS: enzalutamide 36.6 vs placebo 14.7 months;** **27% reduction in risk of death** HR = 0.73 (95% CI: 0.61–0.89) p = 0.001
SPARTAN 2018, 2021 [1204, 1208]	ADT + apalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2 ng/mL PSA-DT ≤ 10 mo.	**72% reduction of distant progression or death** **Median MFS: apalutamide 40.5 vs placebo 16.2 months;** **22% reduction in risk of death** HR = 0.78 (95% CI: 0.64–0.96) p = 0.0161

ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; nmCRPC = non-metastatic castrate-resistent prostate cancer; PSA-DT = prostate-specific antigen doubling time.

*6.5.5 **Metastatic CRPC***

The remainder of this section focuses on the management of men with proven mCRPC on conventional imaging.

6.5.5.1 Conventional androgen deprivation in CRPC

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [1209, 1210]. However, in the absence of prospective data, the modest potential benefits of continuing castration outweigh the minimal risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression, therefore, it should be continued in these patients.

*6.5.6 **First-line treatment of metastatic CRPC***

6.5.6.1 Abiraterone

Abiraterone was evaluated in 1,088 chemo-naive, asymptomatic or mildly symptomatic mCRPC patients in the phase III COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [1211]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and rPFS were the co-primary endpoints. After a median follow-up of 22.2 months there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, $p < 0.001$) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93, $p = 0.0033$) [1212]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone, but mostly grade 1–2. Subset analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [1213].

6.5.6.2 Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [1214]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naive mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186, CI: 0.15–0.23, $p < 0.0001$), and OS (HR: 0.706, CI: 0.6–0.84, $p < 0.001$). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide

was equally effective and well tolerated in men > 75 years [1215] as well as in those with or without visceral metastases [1216]. However, for men with liver metastases, there seemed to be no discernible benefit [1216, 1217].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double blind phase II study (TERRAIN) showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44, p < 0.0001) in favour of enzalutamide [1217]. With extended follow-up and final analysis the benefit in OS and rPFS were confirmed [1218].

6.5.6.3 Docetaxel

A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxel-based chemotherapy compared to mitoxantrone plus prednisone [1219, 1220]. The standard first-line chemotherapy is docetaxel 75 mg/m^2, 3-weekly doses combined with prednisone 5 mg twice a day (BID), up to 10 cycles. Prednisone can be omitted if there are contraindications or no major symptoms. The following independent prognostic factors: visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help stratify the response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), and show three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [1221].

Age by itself is not a contraindication to docetaxel [1222] but attention must be paid to careful monitoring and co-morbidities as discussed in Section 5.4 - Estimating life expectancy and health status [1223]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m^2 every two weeks seems to be well tolerated with less grade 3–4 AEs and a prolonged time to treatment failure [1224].

6.5.6.4 Sipuleucel-T

In 2010 a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [1225]. After a median follow-up of 34 months, the median survival was 25.8 months in the sipuleucel-T group compared to 21.7 months in the placebo group, with a HR of 0.78 (p = 0.03). No PSA decline was observed and PFS was similar in both arms. The overall tolerance was very good, with more cytokine-related AEs grade 1–2 in the sipuleucel-T group, but the same grade 3–4 AEs in both arms. Sipuleucel-T is not available in Europe.

6.5.6.5 Ipatasertib

The AKT inhibitor ipatasertib in combination with AAP was studied in asymptomatic or mildly symptomatic patients with and without PTEN loss by IHC and previously untreated for mCRPC. The randomised phase III trial (IPAtential) showed a significant benefit for the first endpoint rPFS in the PTEN loss (IHC) population (18.5 vs. 16.5 mo; p = 0,0335, HR: 0.77, 95% CI: 0.61–0,98). The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhoea [818]. Grade 3 or higher AEs occurred nearly double as often in the combination group and the discontinuation rate due to AEs was 4 times higher. This combination is still investigational [1226].

Table 6.5.2: Randomised phase III controlled trials - first-line treatment of mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [1227]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		**OS: 17.52 vs. 15.6 mo.** (p = 0.02, HR: 0.80; 95% CI: 0.67-0.97) **PFS: 6.3 vs. 3.2 mo.** (p < 0.001)
TAX 327 2004, 2008 [1219, 1228]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, Prednisone 5 mg BID		**OS: 19.2 for 3 weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.** (p = 0.004, HR: 0.79, 95% CI: 0.67-0.93)

ABIRATERONE				
COU-AA-302 2013, 2014, 2015 [1211, 1212, 1229]	abiraterone + prednisone	placebo + prednisone	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - No visceral metastases.	**OS: 34.7 vs. 30.3 mo.** (HR: 0.81, p = 0.0033). **FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.** (p < 0.0001)
ENZALUTAMIDE				
PREVAIL 2014 [1214]	enzalutamide	placebo	- No previous docetaxel. - ECOG 0-1. - PSA or radiographic progression. - No or mild symptoms. - 10% had visceral mets.	**OS: 32.4 vs. 30.2 mo.** (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60-0.84) **rPFS: 20.0 mo. vs. 5.4 mo.** HR: 0.186 (95% CI: 0.15-0.23) p < 0.0001)
SIPULEUCEL-T				
IMPACT2010 [1225]	sipuleucel-T	placebo	- Some with previous docetaxel. - ECOG 0-1. - Asymptomatic or minimally symptomatic.	**OS: 25.8 vs. 21.7 mo.** (p = 0.03 HR: 0.78, 95% CI: 0.61-0.98). **FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo.** (no difference)
2006 [1230]	sipuleucel-T	placebo	- ECOG 0-1. - No visceral met. - No corticosteroids.	**OS: 25.9 vs. 21.4 mo.** (p = 0.1). FU: 36 mo. **PFS: 11.7 vs. 10.0 wk.**
IPATASERTIB				
IPAtential150 2021 [1226]	ipatasertib (400 mg/d) + abiraterone (1000 mg/d) + prednisone (5 mg bid)	abiraterone + prednisolone + placebo	Previously untreated for mCRPC, asymptomatic/ mildly symptomatic, with and without PTEN loss by IHC	**rPFS in PTEN loss (IHC) population: 18.5 vs. 16.5 mo.** (p = 0.0335, HR: 0.77 95% CI: 0.61-0.98)

BID = twice a day; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; mets. = metastases; mo = month; (r)PFS = (radiographic) progression-free survival; OS = overall survival; IHC = immunohistochemistry.

*6.5.7 **Second-line treatment for mCRPC and sequence***

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.5.3. High-level evidence exists for second-line treatments after first-line treatment with docetaxel and for third-line therapy.

6.5.7.1 Cabazitaxel

Cabazitaxel is a novel taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [1231]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m^2) plus prednisone (10 mg/day). Overall survival was the primary endpoint which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months, p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3–4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) but also non-haematological (57.4 vs. 39.8%, p < 0.0002) toxicity [1232]. In two post-marketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m^2 cabazitaxel was not inferior to 25 mg/m^2, but less toxic. Therefore, the lower dose should be preferred [1233, 1234]. Cabazitaxel should preferably be given with prophylactic granulocyte colony-stimulating factor (G-CSF) and should be administered by physicians with expertise in handling neutropenia and sepsis [1235].

6.5.7.2 *Abiraterone acetate after prior docetaxel*

Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [1236] and confirmed by the final analysis [1237]. A total of 1,195 patients with mCRPC were randomised 2:1 to AAP or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary endpoint was OS, with a planned HR of 0.8 in favour of AAP. After a median follow-up of 20.2 months, the median survival in the AAP group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, $p < 0.0001$). The benefit was observed in all subgroups and all the secondary objectives were in favour of AAP (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3–4 AEs did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the AAP group, mainly grade 1–2 (fluid retention, oedema and hypokalaemia).

6.5.7.3 *Enzalutamide after docetaxel*

The planned interim analysis of the AFFIRM study was published in 2012 [1238]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary endpoint was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$). This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [1218]. Enzalutamide was active also in patients with visceral metastases.

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.5.7.4 *Radium-223*

The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA) 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo plus SOC. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70, $p < 0.001$) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [1239]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, it did not differ significantly from that in the placebo arm [1239]. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated [1240]. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent [1241]. In particular, the use of radium-223 in combination with AAP showed significant safety risks related to fractures and more deaths. This was most striking in patients without the concurrent use of anti-resorptive agents [1242].

6.5.8 ***Treatment after docetaxel and one line of hormonal treatment for mCRPC***

For men progressing quickly on AR targeted therapy (< 12 months) it is now clear that cabazitaxel is the treatment supported by the best data. The CARD trial, an open label randomised phase III trial, evaluated cabazitaxel after docetaxel and one line of ARTA (either AAP or enzalutamide) [1198]. It included patients progressing in less than 12 months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARTA and reduced the risk of death by 36% vs. ARTA. The rPFS with cabazitaxel remained superior regardless of the ARTA sequence and if docetaxel was given before, or after, the first ARTA.

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open for patients who have a > 12 months response to first-line abiraterone or enzalutamide for mCRPC [1243]. Either radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [1244, 1245] and there is evidence of cross-resistance between enzalutamide and abiraterone [1246, 1247].

In this context, radioligand therapy has been discussed for many years. In pre-treated and highly selected patients, based on PSMA- and FDG PET scan results, ^{117}Lu-PSMA-617 was compared with cabazitaxel in a randomised phase II trial. The primary endpoint PSA reduction ≥ 50% was in favour of the radioligand therapy [1248]. Pivotal phase III data for ^{117}Lu-PSMA-617 are discussed in Section 6.5.9.2.

Poly (ADP-ribose) polymerase inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one ARTA and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate to olaparib [1249] and in another confirmatory trial a confirmed composite response of 54.3% (95% CI: 39.0–69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1–54.6) evaluable patients in the 300 mg cohort [1250].

6.5.8.1 PARP inhibitors for mCRPC

So far, two PARP inhibitors, olaparib and rucaparib, are licenced by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation (e.g., talazoparib, niraparib).

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARTA in mCRPC with alterations in ≥ 1 of any qualifying gene with a role in HRR and progression on an ARTA. Most patients were heavily pre-treated with 1–2 chemotherapies and up to 2 ARTAs [1194, 1195]. Radiographic PFS by blinded independent central review in the *BRCA1/2* or *ATM* mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). The final results for OS demonstrated a significant improvement among men with *BRCA1/2* or *ATM* mutations (Cohort A) (p = 0.0175; HR: 0.69, 95% CI: 0.50– 0.97). This was not significant in men with any (other) HRR alteration (Cohort B) (HR: 0.96, 95% CI: 0.63–1.49). Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 66% (n = 86/131) crossed over to olaparib. When looking specifically at the Cohort B patients, olaparib did not improve rPFS by blinded independent central review (HR: 0.88, 95% CI: 0.58–1.36) or OS (HR: 0.73, 95% CI: 0.45–1.23), however, investigator assessed rPFS demonstrated a benefit for olaparib (HR: 0.60, 95% CI: > 0.39–0.93) [1195, 1251].

The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary to an AE, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This is the first trial to show a benefit for genetic testing and precision medicine in mCRPC.

The olaparib approval by the FDA is for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1* and *BRCA2* alterations [1252]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib has been approved for patients with deleterious *BRCA* mutations (germline and/or somatic) who have been treated with ARTA and a taxane-based chemotherapy [1253]. Approval was not based on OS data but on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious *BRCA* mutations was 43.5% (95% CI: 31–57) [1254].

6.5.8.2 Sequencing treatment

6.5.8.2.1 ARTA -> ARTA (chemotherapy-naive patients)

The use of sequential ARTAs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial [1255-1262]. In particular in patients who had a short response to the first ARTA for mCRPC (< 12 months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present).

In highly selected patients treated for more than 24 weeks with AAP, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1–8.3) and an unconfirmed PSA response rate of 27% [1263]. In case the patient is unfit for chemotherapy and a PARP inhibitor best supportive care should be considered in case no other appropriate treatment option is available (clinical trial or immunotherapy if MSI-high). An ARTA-ARTA sequence should never be the preferred option but might be considered in such patients if the PS still allows for active treatment and the potential side effects seem manageable.

First prospective cross-over data on an ARTA-ARTA sequence [1255] and a systematic review and meta-analysis suggest that for the endpoints PFS and PSA PFS, but not for OS, abiraterone followed by enzalutamide is the preferred choice [1264].

6.5.8.2.2 ARTA -> PARP inhibitor/olaparib

This sequence in patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial [1195]. A subgroup of patients in this trial was pre-treated with one or two ARTAs and no chemotherapy (35%). The ARTA – docetaxel - PARP inhibitor vs. ARTA – PARP inhibitor - docetaxel sequences are still under investigation.

6.5.8.2.3 Docetaxel for mHSPC -> docetaxel rechallenge

There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mHSPC. Docetaxel seems to be less active than ARTA at progression to mCRPC following docetaxel for mHSPC [1265].

6.5.8.2.4 ARTA -> docetaxel or docetaxel -> ARTA followed by PARP inhibitor

Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARTA and docetaxel in either sequence [1195, 1253].

6.5.8.2.5 ARTA before or after docetaxel

There is level 1 evidence for both sequences (see Table 6.5.3).

6.5.8.2.6 ARTA –> docetaxel -> cabazitaxel or docetaxel –> ARTA -> cabazitaxel

Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high-level evidence favouring cabazitaxel vs. a second ARTA after docetaxel and one ARTA. CARD is the first prospective randomised phase III trial addressing this question (see Table 6.5.3) [1198].

Table 6.5.3: Randomised controlled phase II/III - second-line/third-line trials in mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [1237]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel. ECOG 0-2. PSA or radiographic progression.	**OS: 15.8 vs. 11.2 mo.** (p < 0.0001, HR: 0.74, 95% CI: 0.64–0.86; p < 0.0001). FU: 20.2 mo. **rPFS: no change**
COU-AA-301 2011 [1236]				**OS: 14.8 vs. 10.9 mo.** (p < 0.001 HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**
Radium-223				
ALSYMPCA 2013 [1239]	radium-223	placebo	Previous or no previous docetaxel. ECOG 0-2. Two or more symptomatic bone metastases. No visceral metastases.	**OS: 14.9 vs. 11.3 mo.** (p = 0.002, HR: 0.61; 95% CI: 0.46–0.81). All secondary endpoints show a benefit over best SOC.
CABAZITAXEL				
TROPIC 2013 [1266]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel. ECOG 0-2.	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 months OS ≥ 2 yr 27% vs. 16% PFS: -
TROPIC 2010 [1231]				**OS: 15.1 vs. 12.7 mo.** (p < 0.0001, HR: 0.70; 95% CI: 0.59–0.83). FU: 12.8 mo. PFS: 2.8 vs. 1.4 mo. (p < 0.0001, HR: 0.74, 95% CI: 0.64-0.86)

CARD 2019 [1198]	cabazitaxel (25 mg/m^2 Q3W) + prednisone + G-CSF	ARTA: abiraterone + prednisone OR enzalutamide	Previous docetaxel. Progression ≤ 12 mo. on prior alternative ARTA (either before or after docetaxel)	**Med OS 13.6 vs. 11.0 mo.** (p = 0.008, HR: 0.64, 95% CI: 0.46–0.89). **rPFS 8.0 vs. 3.7 mo.** (p < 0.001, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.
ENZALUTAMIDE				
AFFIRM 2012 [1238]	enzalutamide	placebo	Previous docetaxel. ECOG 0-2.	**OS: 18.4 vs. 13.6 mo.** (p < 0.001, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35–0.47, p < 0.0001).
PARP inhibitor				
PROfound 2020 [1194, 1195, 1251]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	Previous ARTA, alterations in HRR mutated genes	**rPFS: 7.39 vs. 3.55 mo.** (p < 0.0001, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). **OS: 19.1 mo vs. 14.7 mo.** (in pts with *BRCA1/2*, *ATM* alterations) (p = 0.0175; HR 0.69, 95% CI: 0.5–0.97).
Radioligand therapy				
VISION 2021 [1267]	^{177}Lu-PSMA-617	^{177}Lu-PSMA-617 + SOC or SOC alone	Previous at least 1 ARTA and one or two taxane regimens; Mandatory: PSMA-positive gallium-68 (^{68}Ga)–labeled PSMA-PET scan	**Imaging-based PFS: 8.7 vs. 3.4 mo.** (p < 0.001; HR 0.40; 99.2% CI: 0.29–0.57) **OS: 15.3 vs. 11.3 mo.** (p < 0.001; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [1248]	^{177}Lu-PSMA-617 (8.5 GBq i.v.q 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	^{177}Lu-PSMA-617 1:1 randomisation cabazitaxel (20 mg/m^2 i.v.q 3-weekly, up to 10 cycles)	mCRPC post docetaxel, suitable for cabaziaxel	**PSA reduction of > 50%:** 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016).

**Only studies reporting survival outcomes as primary endpoints have been included.*
ARTA = androgen receptor targeting agents; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; HR = hazard ratio; Lu = lutetium; mo = months OS = overall survival; OR = odds ratio; ORR = objective response rate; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr = year; HRR= homologous recombination repair.

*6.5.9 **Second-line treatment for mCRPC and sequencing of therapy***

6.5.9.1 Background

During the 90s several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 were developed for the treatment of bone pain secondary to metastasis from PCa [1268]. They were effective at palliation; relieving pain and improving QoL, especially in the setting of diffuse bone metastasis. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223 (see Section 6.5.7.4).

6.5.9.2 PSMA-based therapy

The increasing use of PSMA PET as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope

with a therapeutic isotope which accumulates where the tumour is demonstrated (theranostics) [1269]. Therefore, after identification of the target usually with diagnostic ^{68}Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with β(lutetium-177 or ytrium-90) or α(actinium-225)-emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported with the most robust data is ^{177}Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [1270]. The early data were based on single-centre experience [1271]. Data from uncontrolled prospective phase II trials reported high response rates with low toxic effects [1272, 1273]. Positive signals are also coming from a randomised trial [1248].

In TheraP, a randomised phase II trial, patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by ^{68}Ga-PSMA-11 and ^{18}FDG PET-CT scans, were randomised to receive ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously every 6 weeks for up to 6 cycles) or cabazitaxel (20 mg/m^2 for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for ^{177}Lu–PSMA-617 vs. cabazitaxel, respectively, by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016). Secondary endpoints included ORR, rPFS and PSA FSF as well as QoL [1248].

Finally, an open-label phase III trial (VISION) compared ^{177}Lu–PSMA-617 radioligand therapy with protocol-permitted SOC in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARTA and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. Eligible patients had to present with at least one PSMA-positive metastatic lesion exceeding the uptake of the liver parenchyma on a ^{68}Ga-PSMA-11 PET–CT and without PSMA-negative lesions in any LN with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis.

More than 800 patients were randomised. ^{177}Lu-PSMA-617 plus SOC significantly prolonged both imaging-based PFS and OS as compared with SOC alone (see Table 6.5.3). Grade 3 or above AEs were higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. ^{177}Lu–PSMA-617 has shown to be a valuable additional treatment option in this mCRPC population [1267].

*6.5.10 **Immunotherapy for mCRPC***

The immune checkpoint inhibitor pembrolizumab was approved by the FDA for all *MMR*–deficient cancers or in those with instable microsatellite status (MSI-high) [1196]. This also applies to PCa but it is a very rare finding in this tumour entity [1197]. In all other PCa patients pembrolizumab monotherapy is still experimental. It shows limited anti-tumour activity with an acceptable safety profile, again in a small subset of patients. A phase II trial enrolled 258 patients treated with pembrolizumab [1274]. The objective response rate was around 4%, but those responses were durable. Combination immunotherapy is under investigation.

The CTLA-4 inhibitor ipilimumab was evaluated in docetaxel pre-treated mCRPC patients after RT to bone metastases in a placebo-controlled phase III RCT. Although the trial's primary endpoint OS was not improved significantly, a pre-planned long-term analysis showed that OS rates at 3, 4, and 5 years were approximately two to three times higher in the ipilimumab arm (2 years [25.2% vs. 16.6%], 3 years [15.3% vs. 7.9%], 4 years [10.1% vs. 3.3%], and 5 years [7.9% vs. 2.7%]). These data support the hypothesis that a subset of mCRPC patients might derive a long-term benefit from CTLA-4 inhibition. Further prospective data are needed to support the routine use of ipilimumab [1275]. It has not been approved for the use in PCa management.

*6.5.11 **Platinum chemotherapy***

Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1276]. More recently, the combination of cabazitaxel and carboplatin was evaluated in pre-treated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5–5.7) to 7.3 months (95% CI: 5.5–8.2; HR: 0.69, 95% CI: 0.50–0.95, p = 0.018) and the combination was well tolerated [1277]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including *TP53, RB1*, and *PTEN* [1278].

Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [1279], also after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients as well as patients without DDR gene alterations also showed a

50% PSA decline in up to 36% of patients [1280]. In view of the excellent tolerability of e.g. carboplatin monotherapy, platinum could be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Prospective controlled trials are ongoing.

*6.5.12 **Monitoring of treatment***

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, total testosterone level, full blood count, renal function, baseline liver function tests, alkaline phosphatase), bone scan and CT of chest, abdomen and pelvis [1281, 1282]. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR or hormone-naive disease. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARTA have been described [1283]. Prostate-specific antigen alone is not reliable enough [1284] for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA [1285]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [1220]. A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [1281]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost and patients with no objective benefit should have their treatment modified. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of no longer ‘clinically benefiting‘ to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [1286]. These recommendations also seem valid for clinical practice outside trials.

*6.5.13 **When to change treatment***

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Preferably, any treatment change should precede development of *de novo* symptoms or worsening of existing symptoms. Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore it is not clear how to select the most appropriate ‘second-line‘ treatment, in particular in patients without HRR alterations or other biomarkers. A positive example, however, is the CARD trial which clearly established cabazitaxel as the better third-line treatment in docetaxel pre-treated patients after one ARTA compared to the use of a second ARTA [1198].

The ECOG PS has been used to stratify patients. Generally men with a PS of 0–1 are likely to tolerate treatments and those with a PS of ≥ 2 are less likely to benefit. However, it is important that treatment decisions are individualised, in particular when symptoms related to disease progression are impacting on PS. In such cases, a trial of active life-prolonging agents to establish if a given treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in a summary paper published following the 2019 APCCC Conference [1287].

*6.5.14 **Symptomatic management in metastatic CRPC***

Castration-resistant PCa is usually a debilitating disease often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [1287, 1288]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

6.5.14.1 Common complications due to bone metastases

Most patients with CRPC have painful bone metastases. External beam RT is highly effective, even as a single fraction [1289, 1290]. A single infusion of a third generation bisphosphonate could be considered when RT is not available [1291]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture whatever its origin, clearly improving both pain and QoL [1292]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1293, 1294]. Impending spinal cord compression is an emergency. It must be recognised early and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT [1295]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

6.5.14.2 Preventing skeletal-related events

6.5.14.2.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anti-cancer treatments, but for docetaxel, were available. Six hundred and forty three patients who had CRPC with bone metastases were randomised to receive zoledronic acid, 4 or 8 mg every three weeks for 15 consecutive months, or placebo [1296]. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at 15 and 24 months of follow-up, patients treated with 4 mg zoledronic acid had fewer SREs compared to the placebo group (44 vs. 33%, p = 0.021) and in particular fewer pathological fractures (13.1 vs. 22.1%, p = 0.015). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.5.14.2.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ-B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, p = 0.028) [1289]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA or the EMA have approved denosumab for this indication [1297].

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with mCRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR: 0.82, p = 0.008). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p < 0.0001 for both). However, these findings were not associated with any survival benefit and in a *post-hoc* re-evaluation of endpoints, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1298].

The potential toxicity (e.g., osteonecrosis of the jaw, hypocalcaemia) of these drugs must always be kept in mind (5–8.2% in M0 CRPC and mCRPC, respectively) [1298-1300]. Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery or dental infection [1301]. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial [1302] (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1297]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy [1303]. Hypocalcaemia should be identified and prevented during treatment with bone protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively) [1300]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU equivalent) are recommended in all patients, unless in case of hypercalcaemia [1300, 1304, 1305].

*6.5.15 **Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant disease***

Summary of evidence	**LE**
First-line treatment for mCRPC will be influenced by which treatments were used when metastatic cancer was first discovered.	4
No clear-cut recommendation can be made for the most effective drug for first-line CRPC treatment (i.e., hormone therapy, chemotherapy or radium-223) as no validated predictive factors exist.	3

Recommendations	**Strength rating**
Ensure that testosterone levels are confirmed to be < 50 ng/dL before diagnosing castrate-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents.	Strong
Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong

6.5.16 *Guidelines for systematic treatments of castrate-resistant disease*

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
Avoid sequencing of androgen receptor targeted agents.	Weak
Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents	
Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong

6.5.17 *Guidelines for supportive care of castrate-resistant disease*

These recommendations are in addition to appropriate systemic therapy.

Recommendations	Strength rating
Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
Treat painful bone metastases early on with palliative measures such as intensity-modulated radiation therapy/volumetric arc radiation therapy plus image-guided radiation therapy and adequate use of analgesics.	Strong
In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

6.5.18 *Guideline for non-metastatic castrate-resistant disease*

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

6.6 Summary of guidelines for the treatment of prostate cancer

Table 6.6.1: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

6.6.1 General guidelines recommendations for treatment of prostate cancer

Recommendations	**Strength rating**
Inform patients that based on robust current data with up to 12 years of follow-up, no active treatment modality has shown superiority over any other active management options or deferred active treatment in terms of overall- and PCa-specific survival for clinically localised low/intermediate-risk disease.	Strong
Offer a watchful waiting policy to asymptomatic patients with clinically localised disease and with a life expectancy < 10 years (based on co-morbidities and age).	Strong
Inform patients that all active local treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Weak
When a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging.	Strong
Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, magnetic resonance imaging, or with this information combined into a nomogram).	Weak
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc radiation therapy (VMAT) plus image-guided radiation therapy (IGRT) for definitive treatment of PCa by external-beam radiation therapy.	Strong
Offer moderate hypofractionation (HFX) with IMRT/VMAT plus IGRT to the prostate to patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks.	Strong
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and low- or intermediate-risk disease with ISUP grade 2 and ≤ 33% of biopsy cores involved.	Strong
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function intermediate-risk disease with ISUP G3 and/or PSA 10–20 ng/mL.	Weak
Offer LDR or HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and high-risk and/or locally advanced disease.	Weak
Active therapeutic options outside surgery or radiotherapy	
Offer whole-gland cryotherapy and high-intensity focused ultrasound within a clinical trial setting or well-designed prospective cohort study.	Strong
Offer focal therapy within a clinical trial setting or well-designed prospective cohort study.	Strong

6.6.2 *Guidelines recommendations for the various disease stages*

Recommendations		Strength rating
Low-risk disease		
Active surveillance (AS)	**Selection of patients**	
	Offer AS to patients with a life expectancy > 10 years and low-risk disease.	Strong
	Patients with intraductal and cribiform histology on biopsy should be excluded from AS.	Strong
	Perform MRI before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
	Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
	If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
	If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
	Follow-up strategy	
	Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
	In case of PSA progression or change in DRE or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong
Active treatment	Offer surgery or radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND.	Strong
Radiotherapeutic treatment	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa and good urinary function.	Strong
	Use intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with a total dose of 74–80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without androgen deprivation therapy (ADT).	Strong
Other therapeutic options	Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Strong
	Only offer whole gland treatment (such as cryotherapy, high-intensity focused ultrasound [HIFU], etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study.	Strong
Intermediate-risk disease		
Active surveillance	Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA <10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
	Patients with ISUP grade group 3 disease must be excluded from AS protocols.	Strong
	Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
Radical Prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease.	Strong

Extended pelvic lymph node dissection (ePLND)	Perform an ePLND in intermediate-risk disease based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2).	Strong
Radiotherapeutic treatment	Offer LDR brachytherapy to patients with good urinary function and favourable intermediate-risk disease.	Strong
	For IMRT/VMAT plus image-guided radiotherapy (IGRT), use a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term ADT (4–6 months).	Strong
	Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Weak
	Offer HDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
	In patients not willing to undergo ADT, use a total dose of IMRT/VMAT plus IGRT (76–78 Gy) or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks) or a combination with LDR or HDR brachytherapy boost.	Weak
Other therapeutic options	Only offer whole-gland ablative therapy (such as cryotherapy, HIFU, etc.) or focal ablative therapy for intermediate-risk disease within a clinical trial setting or well-designed prospective cohort study.	Strong
	Do not offer ADT monotherapy to intermediate-risk asymptomatic men not able to receive any local treatment.	Weak
High-risk localised disease		
Radical prostatectomy	Offer RP to selected patients with high-risk localised PCa, as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatments	In patients with high-risk localised disease, use IMRT)/VMAT plus IGRT with 76–78 Gy in combination with long-term ADT (2 to 3 years).	Strong
	In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	Do not offer either whole gland nor focal therapy to patients with high-risk localised disease.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong
Locally-advanced disease		
Radical prostatectomy	Offer RP th-advanced PCa as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND prior to RP in locally-advanced PCa.	Strong
Radiotherapeutic treatments	Offer patients with locally-advanced disease IMRT/VMAT plus IGRT in combination with long-term ADT.	Strong
	Offer patients with locally advanced disease and good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT.	Weak
	Offer long-term ADT for at least two years.	Weak
	Prescribe 2 years of abiraterone when offering IMRT/VMAT plus IGRT to the prostate plus pelvis (for cN1) in combination with long-term ADT, for M0 patients with cN1 or ≥ 2 high-risk factors (cT3–4, Gleason ≥ 8 or PSA ≥ 40 ng/mL).	Strong

Therapeutic options outside surgery or radiotherapy	Do not offer whole gland treatment or focal treatment to patients with locally-advanced PCa.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSA-doubling time < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms.	Strong
	Offer patients with cN1 disease a local treatment (either RP or IMRT/VMAT plus IGRT) plus long-term ADT.	Weak
Adjuvant treatment after radical prostatectomy		
pN0 & pN1 disease	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Only offer adjuvant IMRT/VMAT plus IGRT to high-risk patients (pN0) with adverse pathology (ISUP grade group 4–5 and pT3 with or without positive margins).	Strong
	Discuss three management options with patients with pN1 disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT; 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT; 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and a PSA < 0.1 ng/mL.	Weak
Non-curative or palliative treatments in a first-line setting		
Localised disease		
Watchful waiting	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
Locally-advanced disease		
Watchful waiting	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA-DT > 12 months, a PSA < 50 ng/mL and well-differentiated tumour who are unwilling or unable to receive any form of local treatment.	Weak
Persistent PSA after radical prostatectomy		
	Offer a prostate-specific membrane antigen positron-emission tomography (PSMA PET) scan to men with a persistent PSA > 0.2 ng/mL if the results will influence subsequent treatment decisions.	Weak
	Treat men with no evidence of metastatic disease with salvage RT and additional hormonal therapy.	Weak

6.6.3 *Guidelines for metastatic disease, second-line and palliative treatments*

Recommendations		Strength rating
Metastatic disease in a first-line setting		
M1 patients	Offer immediate systemic treatment with ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
	Offer luteinising hormone-releasing hormone (LHRH) antagonists or orchiectomy before starting ADT, especially to patients with impending clinical complications like spinal cord compression or bladder outlet obstruction.	Strong
	Offer early systemic treatment to M1 patients asymptomatic from their tumour.	Strong
	Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
	Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
	Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
	Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
	Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
	Offer ADT combined with prostate radiotherapy (RT) (using the doses and template from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
	Do not offer ADT combined with any local treatment (RT/surgery) to patients with high-volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
	Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
	Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong
Biochemical recurrence after treatment with curative intent		
Biochemical Recurrence (BCR) after radical prostatectomy (RP)	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Offer early salvage IMRT/VMAT plus IGRT to men with two consecutive PSA rises.	Strong
	A negative PET/CT scan should not delay salvage radiotherapy (SRT), if otherwise indicated.	Strong
	Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
	Offer hormonal therapy in addition to SRT to men with BCR.	Weak
BCR after RT	Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
	Only offer salvage RP, brachytherapy, HIFU, or cryosurgical ablation to highly selected patients with biopsy-proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres.	Strong
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > 12 months.	Strong

Life-prolonging treatments of castration-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/dL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents.	Strong
	Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability.	Strong
Systemic treatments of castrate-resistant disease		
	Base the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223, sipuleucel-T).	Strong
	Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naive docetaxel with 75 mg/m^2 every 3 weeks.	Strong
	Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair (HRR) alterations.	Strong
	Base further treatment decisions of mCRPC on PS, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference.	Strong
	Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy.	Strong
	Avoid sequencing of androgen receptor targeted agents.	Weak
	Offer chemotherapy to patients previously treated with abiraterone or enzalutamide.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel.	Strong
	Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide.	Strong
Novel agents		
	Offer poly(ADP-ribose) polymerase (PARP) inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations.	Strong
	Offer ^{177}Lu-PSMA-617 to pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.	Strong
Supportive care of castration-resistant disease		
	Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
	Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as IMRT/VMAT plus IGRT and adequate use of analgesics.	Strong
	In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate.	Strong
Non-metastatic castrate-resistant disease		
	Offer apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSA-DT < 10 months) to prolong time to metastases and overall survival.	Strong

7. FOLLOW-UP

The rationale for following up patients is to assess immediate- and long-term oncological results, ensure treatment compliance and allow initiation of further therapy, when appropriate. In addition, follow-up allows monitoring of side effects or complications of therapy, functional outcomes and an opportunity to provide psychological support to PCa survivors, all of which is covered in Chapter 8.

7.1 Follow-up: After local treatment

*7.1.1 **Definition***

Local treatment is defined as RP or RT, either by IMRT plus IGRT or LDR- or HDR-brachytherapy, or any combination of these, including neoadjuvant and adjuvant therapy. Unestablished alternative treatments such as HIFU, cryosurgery and focal therapy options do not have a well-defined, validated, PSA cut-off to define BCR but follow the general principles as presented in this section. In general, a confirmed rising PSA is considered a sign of disease recurrence.

*7.1.2 **Why follow-up?***

The first post-treatment clinic visit focuses on detecting treatment-related complications and assist patients in coping with their new situation apart from providing information on the pathological analysis. Men with PCa are at increased risk of depression and attention for mental health status is required [1306, 1307]. Tumour or patient characteristics may prompt changing the follow-up schedule. Follow-up of men diagnosed with PCa may allow early treatment of disease and treatment-related problems. The use of salvage treatment should be considered in light of the expected life-expectancy, especially when below 10 years in asymptomatic patients.

*7.1.3 **How to follow-up?***

The procedures indicated at follow-up visits vary according to the clinical situation. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications in the post-treatment period is highlighted in Sections 6.1.2.4, 6.1.2.4.3, 6.3.9.2, 6.3.10.2.2, 6.3.11.2 and 8.2. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

7.1.3.1 Prostate-specific antigen monitoring

Measurement of PSA is the cornerstone of follow-up after local treatment. While PSA thresholds depend on the local treatment used, PSA recurrence almost always precedes clinical recurrence [1003, 1308]. The key question is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value (see Section 6.3) [1005]. No prospective studies are available on the optimal timing for PSA testing.

7.1.3.1.1 Active surveillance follow-up

Patients included in an AS programme should be monitored according to the recommendations presented in Section 6.2.2.

7.1.3.1.2 Prostate-specific antigen monitoring after radical prostatectomy

Following RP, the PSA level is expected to be undetectable. Biochemical recurrence is any rising PSA after prostatectomy as defined in Chapter 6. Prostate-specific antigen level is expected to be undetectable 2 months after a successful RP [1309]. Prostate-specific antigen is generally determined every 6 months until 3 years and yearly thereafter but the evidence for a specific interval is low [516] and mainly based on the observation that early recurrences are more likely to be associated with more rapid progression [1005, 1310, 1311]. A rising PSA may occur after longer intervals up to 20 years after treatment and depends on the initial risk group [932]. A yearly PSA after 3 years is considered adequate considering the fact that a longer interval to BCR is correlated with a lower EAU-BCR risk score but around 50% of recurrence should be expected beyond 3 years. As mentioned in Section 6.3.2 no definitive threshold can be given for relapse after RP. Persistently measurable PSA in patients treated with RP is discussed in Section 6.2.6.

Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with a PSA nadir < 0.01 ng/mL have a high (96%) likelihood of remaining relapse-free within 2 years [1312]. In addition, post-RP PSA levels > 0.01 ng/mL in combination with clinical characteristics such as ISUP grade and surgical margin status may predict PSA progression and can be useful to establish follow-up intervals [1311]. However, up to 86% of men were reported to have PSA values below 0.2 ng/mL at 5 years after an initial PSA nadir below 0.1 ng/mL within 6 months after surgery [1313]. Lastly, PSA and associated PSA-DT [1314] calculated prior to 0.2 ng/mL may help identify suitable candidates for early intervention [1315]. Prostate-specific antigen monitoring after salvage

RT to the prostatic fossa is done at similar intervals and an early and rapid PSA rise predicts more rapid progression [1310] and is correlated to metastases-free and PCa-specific survival [1316].

7.1.3.1.3 Prostate-specific antigen monitoring after radiotherapy

Following RT, PSA drops more slowly as compared to post RP. A nadir < 0.5 ng/mL is associated with a favourable outcome after RT although the optimal cut-off value remains controversial [1317]. The interval before reaching the nadir can be up to 3 years, or more. At the 2006 RTOG-ASTRO Consensus Conference the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome (mainly metastases), namely, an increase of 2 ng/mL above the post-treatment PSA nadir [1004]. This definition also applies to patients who received HT [1004].

7.1.3.1.4 Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level although rarely [1318]. However, this has only been proven in patients with unfavourable undifferentiated tumours. Prostate-specific antigen measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT but the role of DRE was questioned since it failed to detect any local recurrence in the absence of a rising PSA in a series of 899 patients [1319]. In a series of 1,118 prostatectomy patients, no local histologically proven recurrence was found by DRE alone and PSA measurement may be the only test needed after RP [1320, 1321].

7.1.3.1.5 Transrectal ultrasound, bone scintigraphy, CT, MRI and PET/CT

Imaging techniques have no place in routine follow-up of localised PCa as long as the PSA is not rising. Imaging is only justified in patients for whom the findings will affect treatment decisions, either in case of BCR or in patients with symptoms (see Section 6.3.4 for a more detailed discussion).

*7.1.4 **How long to follow-up?***

Most patients who fail treatment for PCa do so within 7 years after local therapy [534]. Patients should be followed more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE (if considered) are recommended every 6 months until 3 years and then annually. Whether follow-up should be stopped if PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question.

Risk assessment to predict metastases-free and PCa-specific survival after recurrence after primary treatment may guide individual decisions on a need for longer follow-up [937, 1005, 1322]. Even in men with a PSA-DT less than 10 months after RP who choose to defer treatment, a median metastasis-free survival of 192 months and OS of 204 months from RP was observed, indicating the relatively long disease-free intervals observed in men with a rising PSA after local treatment [1323].

Symptomatic recurrence without a PSA rise is extremely rare, however, the symptoms typical for recurrent disease may vary and are poorly defined by published data. In case of the following symptoms PSA testing should be performed to exclude a possible cancer recurrence in particular in men not followed up by regular testing of their PSA levels: skeletal pain, haematuria, progressive voiding complaints, progressive lower body oedema, progressive bowel complaints or complaints of fatigue, sarcopenia or unexplained weight loss [1324].

*7.1.5 **Summary of evidence and guidelines for follow-up after treatment with curative intent***

Summary of evidence	LE
A rising PSA must be differentiated from a clinically meaningful relapse. The PSA threshold that best predicts further metastases after RP is > 0.4 ng/mL and > NADIR + 2 after IMRT/VMAT plus IGRT (± ADT).	3
Palpable nodules combined with increasing serum PSA suggest at least local recurrence.	2a

Recommendations	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and PSA measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

7.2 Follow-up: During first line hormonal treatment (androgen sensitive period)

7.2.1 Introduction

Androgen deprivation therapy is used in various situations: combined with RT for localised or locally-advanced disease, as monotherapy for a relapse after a local treatment, or in the presence of metastatic disease often in combination with other treatments. All these situations are based on the benefits of testosterone suppression either by drugs (LHRH agonists or antagonists) or orchidectomy. Inevitably, the disease will become castrate-resistant, although ADT will be maintained.

This section addresses the general principles of follow-up of patients on ADT alone. As treatment of CRPC and follow-up are closely linked, Section 6.5.7 includes further information on other drug treatments. Furthermore the specific follow-up needed for every single drug is outside the scope of this text, as is follow-up after chemotherapy.

To detect disease- and treatment-related complaints, regular clinical follow-up is mandatory and cannot be replaced by imaging or laboratory tests alone. Complementary investigations must be restricted to those that are clinically helpful to avoid unnecessary examinations and costs.

7.2.2 Purpose of follow-up

The main objectives of follow-up in patients receiving ADT are to ensure treatment compliance, to monitor treatment response, to detect side effects early, and to guide treatment at the time of CRPC. After the initiation of ADT, it is recommended that patients are evaluated every 3 to 6 months. This must be individualised and each patient should be advised to contact his physician in the event of troublesome symptoms.

7.2.3 General follow-up of men on ADT

Patients under ADT require regular follow-up, including monitoring of serum testosterone, creatinine, liver function and metabolic parameters at 3 to 6 month intervals. Men on ADT can experience toxicity independent of their disease stage.

7.2.3.1 Testosterone monitoring

Testosterone monitoring should be considered standard clinical practice in men on ADT. Many men receiving medical castration will achieve a castrate testosterone level (< 20 ng/dL), and most a testosterone level < 50 ng/dL. However, approximately 13–38% of patients fail to achieve these levels and up to 24% of men may experience temporary testosterone surges (testosterone > 50 ng/dL) during long-term treatment [1309] referred to as 'acute on-chronic effect' or 'breakthrough response' [1325]. Breakthrough rates for the < 20 ng/dL threshold were found to be more frequent (41.3%) and an association with worse clinical outcomes was suggested [1325].

The timing of measurements is not clearly defined. A 3 to 6-month testosterone level assessment has been suggested to ensure castration is achieved (especially during medical castration) and maintained. In case a castrate testosterone level is not reached, switching to another agonist or antagonist or to an orchiectomy should be considered. In patients with a confirmed rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castration-resistant state. Ideally, suboptimal testosterone castrate levels should be confirmed with mass spectrometry or an immunoassay [1326, 1327]. After ADT cessation (intermittent treatment or temporary ADT use as with EBRT) testosterone recovery is dependent on patients age and the duration of ADT [1328, 1329].

7.2.3.2 Liver function monitoring

Liver function tests will detect treatment toxicity (especially applicable for NSAA), but rarely indicate disease progression. Men on combined ADT should have their transaminase levels checked at least yearly but in particular in the first 6 months of treatment initiation since liver function disorders were observed relatively early in the majority of patients in larger trials [1330]. In view of potential liver toxicity a more frequent check is needed with some drugs (like abiraterone acetate) [1331]. Alkaline phosphatase may increase secondary to bone metastases and androgen-induced osteoporosis, therefore it may be helpful to determine bone-specific isoenzymes as none are directly influenced by ADT [1332].

7.2.3.3 Serum creatinine and haematological parameters

Estimated glomerular filtration rate monitoring is good clinical practice as an increase may be linked to ureteral obstruction or bladder retention. A decline in haemoglobin is a known side effect of ADT. A significant decline after 3 months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue although other causes should be considered [1333]. Anaemia is often multi-factorial and other possible aetiologies should be excluded. An early decrease in haemoglobin 3 months after ADT initiation predicted better survival whereas a decrease beyond 6 months was associated with poor outcome in the SPCG-5 population [1334]. Radiotherapy to more extensive bone metastases locations may result in myelosuppression and haematological toxicity [1335, 1336].

7.2.3.4 Monitoring of metabolic complications

The most severe complications of androgen suppression are metabolic syndrome, cardiovascular morbidity, mental health problems, and bone resorption (see Section 8.2.4.5).

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and routinely) in addition to checking blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Prior to starting ADT a cardiology consultation should be considered in men with a history of cardiovascular disease and in men older than 65 years. Men on ADT are at increased risk of cardiovascular problems and hypertension and regular checks are required [1337]. More profound androgen ablation resulted in a higher cardiovascular toxicity [1338] and cardio-respiratory fitness decreased even after 6 months of ADT [1339]. Although LHRH antagonists have been suggested to provide a more favourable cardiovascular toxicity profile compared to LHRH agonists, the prematurely closed PRONOUNCE study found no difference at 12 months in major adverse cardiovascular events between men receiving degarelix or leuprolide [1340].

7.2.3.5 Monitoring bone problems

Androgen deprivation therapy increases the risk of osteoporosis. Administration of ADT for more than a year, as compared to less than one year, showed a higher risk of osteoporosis (HR: 1.77 and 1.38, respectively) [1341]. Several scores (e.g., Fracture Risk Assessment Tool [FRAX score], Osteoporosis Self-Assessment Tool [OST], Osteoporosis Risk Assessment Instrument [ORAI], Osteoporosis Index of Risk [OSIRIS], Osteoporosis Risk Estimation [SCORE]) can help identify men at risk of osteoporotic complications but validation of these scores in the ADT setting is required (see Section 8.3.2.2) [1342-1344].

Routine bone monitoring for osteoporosis should be performed using dual emission X-ray absorptiometry (DEXA) scan [1345-1347]. Presence of osteoporosis should prompt the use of bone protective agents. The criteria for initiation of bone protective agents are mentioned in Section 8.3.2.2. If no bone protective agents are given, a DEXA scan should be done regularly, at least every 2 years [1348].

A review summarising the incidence of bone fractures showed an almost doubling of the risk of fractures when using ADT depending on patients' age and duration and type of ADT with the highest incidence in older men and men on additional novel ARTA medication across the entire spectrum of disease [1349]. In case of an osteoporotic fracture a bone protective agent is mandatory. Vitamin D and calcium levels should be regularly monitored when patients receive ADT and patients should be supplemented if needed. (see Section 8.3.2.2).

7.2.3.6 Monitoring lifestyle, cognition and fatigue

Lifestyle (e.g., diet, exercise, smoking status, etc.) affects QoL and potentially outcome [1332, 1333]. During follow-up men should be counselled on the beneficial effects of exercise to avoid ADT-related toxicity [1350]. Androgen deprivation therapy may affect mental and cognitive health and men on ADT are three times more likely to report depression [1351]. Attention to mental health should therefore be an integral part of the follow-up scheme. Men on ADT may experience complaints of fatigue possibly related to systemic inflammation [1352]. Cognitive performance and fatigue may arise within 6 months after initiation of ADT but can increase over time [1353]. These aspects affect patients as well as their partners and couple counselling should be considered [1354].

7.2.4 ***Methods of follow-up in men on ADT without metastases***

7.2.4.1 Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive non-metastasised PCa. Imaging should be considered when PSA is rising > 2 ng/mL or in case of symptoms suggestive of metastasis.

7.2.4.2 Imaging

In general, asymptomatic patients with a stable PSA level do not require further imaging, although care needs to be taken in patients with aggressive variants when PSA levels may not reflect tumour progression [1355]. New bone pain requires at least targeted imaging and potentially a bone scan. When PSA progression suggests CRPC status and treatment modification is considered, imaging, by means of a bone and CT scan, is recommended for restaging. Detection of metastases greatly depends on imaging (see Section 6.3.4).

7.2.5 ***Methods of follow-up in men under ADT for metastatic hormone-sensitive PCa***

In metastatic patients it is of the utmost importance to counsel about early signs of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk. The intervals for follow-up in M1 patients should be guided by patients' complaints and can vary. Since most men will receive another anti-cancer therapy combined with ADT such as ARTA, chemotherapy or local RT, follow-up frequency should also be dependent on the treatment modality.

7.2.5.1 PSA monitoring

In men on ADT alone, a PSA decline to < 4 ng/mL suggests a likely prolonged response and follow-up visits may be scheduled every 3 to 6 months provided the patient is asymptomatic or clinically improving. This applied to men on ADT monotherapy as well as after ADT plus docetaxel [1151]. Depending on symptoms and risk assessment, more frequent visits may be indicated. Treatment response may be evaluated based on a change in serum PSA level [1150, 1151] and bone- and CT scan although there is no consensus about how frequently these should be performed [1287]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. A rising PSA should prompt assessment of testosterone level, which is mandatory to define CRPC status, as well as restaging using imaging. However, it is now recognised that a stable PSA during ADT is not enough to characterise a non-progressive situation [1356].

7.2.5.2 Imaging as a marker of response in metastatic PCa

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used in bone where response assessment is difficult [1357, 1358].

When bone scan is used to follow bone metastases, a quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1359]. Nonetheless, bone scan is limited by the so-called 'flare' phenomenon which is defined by the development of new images induced by treatment on a first follow-up scan which, after longer observation, actually represent a favourable response. Flare is observed within 8 to 12 weeks of treatment initiation and can lead to a false-positive diagnosis of disease progression. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. Magnetic resonance imaging can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available [1360]. The ability of PET/CT to assess response has been evaluated in a few studies. Until further data are available, MRI and PET/CT should not be used outside trials for treatment monitoring in metastatic patients [1361].

Men with metastasised PCa on ADT should also in the absence of a PSA rise be followed up with regular imaging since twenty-five percent of men with, or without, docetaxel in the CHAARTED trial developed clinical progression without a PSA rise [1356]. One in eight men with a PSA < 2 ng/mL showed clinical progression[1356]. The addition of docetaxel to ADT in the CHAARTED trial population did not reduce the incidence of clinical progression at low PSA values and this rate was similar for both low- and high-volume disease as per CHAARTED criteria [1356]. However, the optimal timing and image modality to be used remain unclear, as is the real clinical value of any findings.

*7.2.6 **Guidelines for follow-up during hormonal treatment***

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every 3–6 months.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong
As a minimum requirement, include a disease-specific history, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level measurements.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50 ng/dL (< 1.7 nmol/L).	Strong

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first (Section 8.2) will summarise long-term consequences (≥ 12 months) of therapies for PCa. Based on two systematic reviews, the second (Section 8.3) provides evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and also supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1 Introduction

Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as close relations and work or vocation. These multifaceted issues all have a bearing on an individual's perception of QoL [1362]. Approaching care from a holistic point of view requires the intervention of a multi-disciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others including fellow patients. Attention to the psychosocial concerns of people with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1363]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Psychological distress can be caused by the cancer diagnosis itself, cancer symptoms and/or treatment side effects [1364]. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed. Cross-sectional patient-reported outcomes studies in general PCa populations show the impact of treatment on global and disease-specific QoL is greater than that described in clinical trial populations who often have less co-morbidity and belong to higher socio-economic groups. Individuals undergoing two or more treatments have more symptoms and greater impact on QoL [1365, 1366].

8.2 Adverse effects of PCa therapies

*8.2.1 **Surgery***

A lack of clear consensus in reporting surgical complications following RP, specifically urinary incontinence and stricture rates, and the introduction of different techniques has resulted in a wide variation in the types of complications reported, as well as variation in the overall incidence of complications [1367-1370]. The most common post-operative complication is ED but other related issues to consider include dry ejaculation, which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [1371]. The second most commonly occurring complication is long-term incontinence [1367-1370] but voiding difficulties may also occur associated with bladder neck contracture (e.g., 1.1% after RALP) [1372].

For those undergoing minimally invasive procedures port site hernia has been reported in 0.66% after inserting 12 mm bladeless trocar and can occur more rarely with 8 mm and 5 mm trocars [1373]. A key consideration is whether long-term consequences of surgery are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [555, 645-648], and can be compared with contemporaneous reports after RRP [649]. From these reports, the mean continence rates at 12 months were 89–100% for patients treated with RALP and 80–97% for patients treated with RRP. A prospective controlled non-randomised trial of patients undergoing RP in 14 centres using RALP or RRP demonstrated that at 12 months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The unadjusted OR was 1.08 (95% CI: 0.87–1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The unadjusted OR was 0.81 (95% CI: 0.66–0.98) [650, 1374]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1374, 1375]. A single-centre randomised phase III study comparing RALP and RRP (n = 326) also demonstrates similar functional outcomes with both techniques at 24 months [550]. Prostatectomy was found to increase the risk of complaints from an inguinal hernia, in particular after an open procedure when compared to minimal invasive approaches [1376, 1377].

*8.2.2 **Radiotherapy***

8.2.2.1 Side-effects of external beam radiotherapy

Analysis of the toxicity outcomes of the ProtecT trial shows that patients treated with EBRT and 6 months of ADT report bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding (described in detail in Section 8.3.1.1 below) [1378]. Participants in the ProtecT study were treated with 3D-CRT and more recent studies using IMRT demonstrate less bowel toxicity than noted previously with 3D-CRT [1379].

A systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrates an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62) with similar risks over lag times of

5 and 10 years. Absolute excess risks over 10 years are small (1–4%) but should be discussed with younger patients in particular [1380].

8.2.2.2 Side effects from brachytherapy

Some patients experience significant urinary complications following implantation such as urinary retention (1.5-22%), with post-implantation TURP reported as being required in up to 8.7% of cases, and incontinence (0–19%) [1381]. Chronic urinary morbidity is more common with combined EBRT and BT and can occur in up to 20% of patients, depending on the severity of the symptoms before brachytherapy. Urethral strictures account for at least 50% of urinary complications and can be resolved with dilation in the majority [763, 769]. Prevention of morbidity depends on careful patient selection and IPSS score, backed up by urodynamic studies.

*8.2.3 **Local primary whole-gland treatments other than surgery or radiotherapy***

8.2.3.1 Cryosurgery

In Ramsay *et al.*'s systematic review and meta-analysis there was evidence that the rate of urinary incontinence at one year was lower for cryotherapy than for RP, but the size of the difference decreased with longer follow-up [827]. There was no significant difference between cryotherapy vs. EBRT in terms of urinary incontinence at one year (< 1%); cryotherapy had a similar ED rate (range 0–40%) to RP at one year. There were insufficient data to compare cryotherapy vs. EBRT in terms of ED.

8.2.3.2 High-intensity focused ultrasound

In terms of toxicity there are insufficient data on urinary incontinence, ED or bowel dysfunction to draw any conclusions, although at one year HIFU had lower incontinence rates than RP (OR: 0.06, 95% CI: 0.01–0.48) [827].

*8.2.4 **Hormonal therapy***

A summary of impacts on psychological factors due to the use of ADT such as sexual function, mood, depression, cognitive function and impact on partners can be found in two clinical reviews [1382, 1383].

A small RCT evaluated the QoL at one-year follow-up in patients with non-localised PCa, between various ADT regimens, or no treatment. Patients treated by ADT reported a significant decline in spatial reasoning, spatial abilities and working memory as well as increased depression, tension, anxiety, fatigue and irritability during treatment [1384]. Conversely, a prospective observational study with follow-up to 3 years failed to demonstrate an association with cognitive decline in men on ADT when compared to men with PCa not treated with ADT and healthy controls [1385]. A prospective observational study of non-metastatic PCa found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [1386]. Another retrospective non-randomised study suggested that men receiving LHRH agonists reported more worry and physical discomfort and poorer overall health, and were less likely to believe themselves free of cancer than patients undergoing orchiectomy. The stage at diagnosis had no effect on health outcomes [1387].

Using a specific non-validated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (not sexual function) at 12 months [1388]. A *post-hoc* analysis, including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [1389], preserved libido and erectile function [1390]. Intermittent androgen deprivation has been discussed elsewhere (see Section 6.4.3.2).

8.2.4.1 Sexual function

Cessation of sexual activity is very common in people undergoing ADT, affecting up to 93% [1391]. Androgen deprivation therapy reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1392].

8.2.4.2 Hot flushes

Hot flushes are a common side-effect of ADT (prevalence estimated between 44–80% of men on ADT) [1391]. They appear 3 months after starting ADT, usually persist long-term and have a significant impact on QoL.

Serotonin re-uptake inhibitors (e.g., venlafaxine or sertraline) also appear to be effective in men but less than hormone therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [1393]. After 6 months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, venlafaxine was inferior -47.2% (interquartile range -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group.

With a placebo effect influencing up to 30% of patients [1394], the efficacy of clonidine, veralipride,

gabapentine [1395] and acupuncture [1396] need to be compared in prospective RCTs.

8.2.4.3 Non-metastatic bone fractures

Due to increased bone turnover and decreased bone mineral density (BMD) in a time-dependent manner, ADT use is linked to an increased risk of fracture (up to 45% RR with long-term ADT) [1397]. Severe fractures in men are associated with a significant risk of death [1398]. A precise evaluation of BMD should be performed by DEXA, ideally before or shortly after starting long-term ADT. An initial low BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of subsequent non-metastatic fracture and causes should be investigated. Other risk factors include increasing age, body mass index of 19 or less, history of previous fracture or parent with fractured hip, current smoking, use of glucocorticoids, rheumatoid arthritis, alcohol consumption > 2 units per day, history of falls and a number of other chronic medical conditions [1399]. Fracture risk algorithms which combine BMD and clinical risk factors such as FRAX score can be used to guide treatment decisions but uncertainty exists regarding the optimal intervention threshold, therefore no specific risk algorithm can be recommended for men on ADT for PCa. Obesity (increase in body fat mass by up to 10% and/or body mass index > 30) and sarcopenia (decrease in lean tissue mass by up to 3%) as well as weight loss are common and occur during the first year of ADT [1400]. These changes increase the fracture risk [1401].

Bicalutamide monotherapy may have less impact on BMD but is limited by its suboptimal efficacy [1402, 1403] (see Section 6.1.4.1.1.5.2.3). The intermittent LHRH-agonist modality might be associated with less bone impact [1404].

8.2.4.4 Metabolic effects

Lipid alterations are common and may occur as early as the first 3 months of treatment [1400]. Androgen deprivation therapy also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [1405], but there is insufficient data to recommend its use in non-diabetic patients.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. The definition requires at least three of the following criteria [1406]:

- waist circumference > 102 cm;
- serum triglyceride > 1.7 mmol/L;
- blood pressure > 130/80 mmHg or use of medication for hypertension;
- high-density lipoprotein (HDL) cholesterol < 1 mmol/L;
- glycaemia > 5.6 mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher during ADT compared with men not receiving ADT [1407]. Skeletal muscle mass heavily influences basal metabolic rate and is in turn heavily influenced by endocrine pathways [1408]. Androgen deprivation therapy-induced hypogonadism results in negative effects on skeletal muscle health. A prospective longitudinal study involving 252 men on ADT for a median of 20.4 months reported lean body mass decreases progressively over 3 years; 1.0% at one year, 2.1% at 2 years, and 2.4% at 3 years which appears more pronounced in men at ≥ 70 years of age [1409].

8.2.4.5 Cardiovascular morbidity

Cardiovascular mortality is a common cause of death in PCa patients [1140, 1410, 1411]. Several studies showed that ADT after only 6 months was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1412]. The RTOG 92-02 [1413] and 94-08 [1414] trials confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. No increase in cardiovascular mortality has been reported in a systematic meta-analysis of trials RTOG 8531, 8610, 9202, EORTC 30891 and EORTC 22863 [1415]. However, serious concerns about the conclusions of this meta-analysis have been raised due to poor consideration of bias in the included studies [1416, 1417]. A meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease patients treated for PCa, e.g. the associations between GnRH agonists and nonfatal or fatal myocardial infarction or stroke RR: 1.57 (95% CI: 1.26–1.94) and RR: 1.51 (95% CI: 1.24–1.84), respectively [1418]. An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1419] or presenting with a metabolic syndrome [1420]. It has been suggested that antagonists might be associated with less cardiovascular morbidity compared to agonists, but, as yet, there is no definite evidence [1340]. In a phase III RCT the use of relugolix, an oral LHRH antagonist, was associated with a reduced risk of major adverse cardiovascular events when compared to leuprolide, an injectable LHRH agonists, at 2.9% vs.

6.2%, respectively, over a follow-up time of 48 weeks (HR 0.46, 95% CI: 0.24–0.88 [795].

These concerns about LHRH agonists resulted in an FDA warning and consensus paper from the American Heart, Cancer Society and Urological Associations [1139]. Preventive advice includes non-specific measures such as loss of weight, increased exercise, minimising alcohol intake, improved nutrition and smoking cessation [71, 1421].

8.2.4.6 Fatigue

Fatigue often develops as a side-effect of ADT. Regular exercise appears to be the best protective measure. Reporting clinically significant fatigue is associated with severe psychological distress and should prompt screening for anxiety and/or depression [1422]. Anaemia may be a cause of fatigue [1391, 1423]. Anaemia requires an aetiological diagnosis (medullar invasion, renal insufficiency, iron deficiency, chronic bleeding) and individualised treatment. Iron supplementation (using injectable formulations only) must be systematic if deficiency is observed. Regular blood transfusions may be required in patients with severe anaemia. Erythropoiesis-stimulating agents might be considered in dedicated cases, taking into account the possible increased risk of thrombovascular events [1424].

8.2.4.7 Neurological side effects

Castration seems also to be associated with an increased risk of stroke [1425], and is suspected to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1426].

8.3 Overall quality of life in men with PCa

Living longer with PCa does not necessarily equate to living well [1362, 1363]. There is clear evidence of unmet needs and ongoing support requirements for some individuals after diagnosis and treatment for PCa [1427]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety and stress in caregivers [1428]. Radical treatment for PCa can negatively impact long-term QoL (e.g., sexual, urinary and bowel dysfunction) as can ADT used in short- or long-term treatment, e.g., sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae and increased cardiovascular and bone fracture risk [1382, 1429]. Direct symptoms from advanced or metastatic cancer, e.g., pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1430, 1431]. Patients' QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1432, 1433].

The concept of 'quality of life' is subjective and can mean different things to different people, but there are some generally common features across virtually all patients. Drawing from these common features, specific tools or 'patient-reported outcome measures' (PROMs) have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores which reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated systematic reviews around cancer-specific QoL outcomes in patients with PCa as the foundation for our guideline recommendations, the following validated PROMs were found in our searches (see Table 8.3.1).

The tools with the best evidence for psychometric properties and feasibility for use in routine practice and research settings to assess PROMs in patients with localised PCa were EORTC QLQ-C30 and QLQ-PR25. Since EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25 module [1434].

Table 8.3.1: PROMs assessing cancer specific quality of life

Questionnaire	Domains/items
Functional Assessment of Cancer Therapy-General (FACT-G) [1435]	Physical well-being, social/family well-being, emotional well-being, and functional well-being.
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1436]	12 cancer site specific items to assess for prostate-related symptoms. Can be combined with FACT-G or reported separately.

European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [1437]	Five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); global health status/QoL scale; and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [1438]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Expanded prostate cancer index composite (EPIC) [1439]	Urinary, bowel, sexual, and hormonal symptoms.
Expanded prostate cancer index composite short form 26 (EPIC 26) [1440]	Urinary, sexual, bowel, and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1441]	Urinary, bowel, and sexual domains.
Prostate Cancer Quality of Life Instrument (PCQoL) [1442]	Urinary, sexual, and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instrument [1443]	Urinary, bowel, and sexual domains.

*8.3.1 **Long-term (> 12 months) quality of life outcomes in men with localised disease***

8.3.1.1 Men undergoing local treatments

The results of the ProtecT trial (n = 1,643 men) reported no difference in EORTC QLQ-C30 assessed global QoL, up to 5 years of follow-up in men aged 50–69 years with T1–T2 disease randomised for treatment with AM, RP or RT with 6 months of ADT [1378]. However, EPIC urinary summary scores (at 6 years) were worse in men treated with RP compared to AM or RT (88.7 vs. 89.0 vs. 91.4, respectively) as were urinary incontinence (80.9 vs. 85.8 vs. 89.4, respectively) and sexual summary, function and bother scores (32.3 vs. 40.6 vs. 41.3 for sexual summary, 23.7 vs. 32.5 vs. 32.7 for sexual function and 51.4 vs. 57.9 vs. 60.1 for sexual bother, respectively) at 6 years of follow-up. Minimal clinically important differences for the 50 item EPIC questionnaire are not available. For men receiving RT with 6 months of ADT, EPIC bowel scores were poorer compared to AM and RP in all domains: function (90.8 vs. 92.3 vs. 92.3, respectively), bother (91.7 vs. 94.2 vs. 93.7, respectively) and summary (91.2 vs. 93.2 vs. 93.0, respectively) at 6 years of follow-up in the ProtecT trial.

The findings regarding RP and RT are supported by other observational studies [1370, 1444]. The Prostate Cancer Outcomes Study (PCOS) studied a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT [1370]. The study reported that at 5 years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However, despite these differences detected at 5 years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at 15 years. More recently, investigators reported that although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance 12 months after treatment [1379]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side effects is reduced with IMRT compared to older 3D-CRT techniques. This is supported by a contemporary 5-year prospective, population-based cohort study where PROMs were compared in men with favourable- and unfavourable-risk localised disease [1444]. In the 1,386 men with favourable risk, comparison between AS and nerve-sparing prostatectomy, EBRT or LDR brachytherapy demonstrates that surgery is associated with worse urinary incontinence at 5 years and sexual dysfunction at 3 years when compared to AS. External beam RT is associated with changes not clinically different from AS, and LDR brachytherapy is associated with worse irritative urinary-, bowel- and sexual symptoms at one year. In 619 men with unfavourable-risk disease, comparison between non-nerve sparing RP and EBRT with ADT demonstrates that surgery is associated with worse urinary incontinence and sexual function through 5 years.

With respect to brachytherapy cancer-specific QoL outcomes, one small RCT (n = 200) evaluated bilateral nerve-sparing RP and brachytherapy in men with localised disease (up to T2a), which reported worsening of physical functioning as well as irritative urinary symptomatology in 20% of brachytherapy patients at one year of follow-up. However, there were no significant differences in EORTC QLQ-C30/PR-25 scores at 5 years of follow-up when compared to pre-treatment values [1445]. It should be noted of this trial, within group tests only were reported. In a subsequent study by the same group comparing bilateral nerve-sparing RARP and brachytherapy (n = 165), improved continence was noted with brachytherapy in the first 6 months but lower potency rates up to 2 years [1446]. These data and a synthesis of 18 randomised and non-randomised studies in a systematic review involving 13,604 patients are the foundation of the following recommendations [1447].

8.3.1.2 *Guidelines for quality of life in men undergoing local treatments*

Recommendations	Strength rating
Advise eligible patients for active surveillance that global quality of life is equivalent for up to 5 years compared to radical prostatectomy or external beam radiotherapy (RT).	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of RT on bowel function with patients.	Strong
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after 5 years.	Weak

8.3.2 ***Improving quality of life in men who have been diagnosed with PCa***

8.3.2.1 *Men undergoing local treatments*

In men with localised disease, nurse-led multi-disciplinary rehabilitation (addressing sexual functioning, cancer worry, relationship issues, depression, managing bowel and urinary function problems) provided positive short-term effects (4 months) on sexual function (effect size 0.45) and long-term (12 months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [1448].

Exercise programs during RT combined with ADT result in consistent benefits for cardiovascular fitness (standardised mean difference [SMD], 0.83; 95% CI: 0.31–1.36; $p < 0.01$) and muscle function (SMD, 1.30; 95% CI: 0.53–2.07; $p < 0.01$) with a reduction in urinary toxicity (SMD, -0.71; 95% CI: -1.25 to -0.18; $p < 0.01$) [1449].

Evidence of moderate quality shows that supervised exercise therapy probably is superior to no exercise therapy in improving 'disease-specific quality of life' and 'walking performance' in patients with PCa undergoing ADT. The results apply to all patients receiving ADT regardless of cancer stage [1450].

In men with post-surgical urinary incontinence, conservative management options include pelvic floor muscle training with or without biofeedback, electrical stimulation, extra-corporeal magnetic innervation (ExMI), compression devices (penile clamps), lifestyle changes, or a combination of methods. Uncertainty around the effectiveness and value of these conservative interventions remains [1451]. Surgical interventions including sling and artificial urinary sphincter significantly decrease the number of pads used per day and increase the QoL compared with before intervention. The overall cure rate is around 60% and results in improvement in incontinence by about 25% [1452].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single centre, double blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [1453]. However, a multi-centre double blind RCT (n = 423) in men aged < 68 years, with normal pre-treatment erectile function undergoing either open, conventional or robot-assisted laparoscopic nerve-sparing RP, tadalafil (5 mg) once per day improved participants EPIC sexual domain-scores (least squares mean difference +9.6, 95% CI: 3.1–16.0) when compared to 20 mg 'on demand' or placebo at 9 months of follow-up [678]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation [1454]. A detailed discussion can be found in the EAU Sexual and Reproductive Health Guidelines [1455].

8.3.2.2 *Men undergoing systemic treatments*

Similar to men treated with a radical approach (see above), in men with T1-T3 disease undergoing RT and ADT, a combined nurse-led psychological support and physiotherapist-led multi-disciplinary rehabilitation has reported improvements in QoL. Specifically this intervention involved action planning around patients' needs related to lifestyle changes, weight control, toilet habits, sexuality, and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5, 95% CI: 0.6–8.4), irritative (adjusted mean 5.8, 95% CI: 1.4–10.3) and hormonal (adjusted mean 4.8, 95% CI: 0.8–8.8) EPIC domains were found up to 22 weeks of follow-up [1456]. In a 3-year follow-up with 92% response rate from the initial study, fewer participants had moderate-severe bowel problems in the intervention (n = 2; 3%) vs. control group (n = 10; 14%) ($p = 0.016$) but the benefits in terms of urinary function were maintained only in those participants with moderate-severe urinary problems at baseline [1457].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8, 95% CI: 6.6–24.9) and cognitive domain outcomes (adjusted mean 11.4, 95% CI: 3.3–19.6) as well as symptom scales for fatigue (adjusted mean 11.0, 95% CI: 20.2–1.7), nausea (adjusted mean 4.0, 95% CI: 7.4–0.25), and dyspnoea (adjusted mean 12.4, 95% CI: 22.5–2.3) up to 3 months in men treated with ADT [1458]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9, 95% CI: 3.7–14.2) in men on long-term ADT [1459, 1460]. These findings are supported by a systematic review which reported improvements up to 12 weeks in cancer-specific

QoL in a meta-analysis of high quality trials (SMD 0.33, 95%, CI: 0.08–0.58) [1423]. Supervised exercise interventions delivered over 12 months are effective in reducing psychological distress; particularly in those men with highest levels of baseline anxiety and depression [1461]. In untrained older men, systematic review suggests lower volume exercise programs at moderate-to-high intensity are as effective as higher volume resistance training for enhancing body composition, functional capacity and muscle strength and may reduce barriers to exercise and enhance adherence [1462].

If dietary intake is not adequate, vitamin D and calcium supplementation should be offered, as there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [1463]. Online tools are available to calculate daily calcium intake for individual patients. For vitamin D deficiency a dose of at least 800 IU/day colecalciferol can be recommended. Use of a 25(OH) assay may be helpful to measure vitamin D levels [1464, 1465].

Anti-resorptive therapy is recommended for men on ADT for > 6 months with either a BMD T score of < -2.5 or with an additional risk factor for osteoporosis or annual bone loss confirmed to exceed 5%, or in cases of severe fracture. Referral to a bone specialist should be considered in complex cases with severe fracture and/or multiple risk factors. Alendronate, risedronate, zoledronate and denosumab have all been shown to prevent bone loss in men with hormone-sensitive locally-advanced and metastatic PCa on ADT [1466-1469]. Patients should be warned about the < 5% risk of osteonecrosis of the jaw and/or atypical femoral fractures associated with these drugs. Bisphosphonates increase BMD in the hip and spine by up to 7% in one year [1468, 1470]. The optimal regimen for zoledronic acid for men on ADT with hormone-sensitive locally-advanced and metastatic PCa remains unclear: quarterly [1471] or yearly [1472] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1473]. A quarterly regimen should be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [1474, 1475]. Care should be taken when discontinuing treatment as rebound increased bone resorption can occur.

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after 2 years, using a 60 mg subcutaneous regimen every 6 months [1476]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, p = 0.006). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120 mg every 4 weeks), a delay in bone metastases of 4.2 months has been shown [1298] without any impact on OS, but with an increase in side effects. Therefore, this later regimen cannot be recommended.

8.3.2.3 Decision regret

Several treatments with curative intent for localised PCa are available all with comparable 10-year OS [516]. They vary in terms of the incidence of major side effects, including urinary symptoms, bowel symptoms and compromised sexual functioning [1378, 1379, 1477]. For this reason, patients' treatment preferences, in which they weigh expected benefits against likely side effects, are a central consideration in shared decision-making and in making informed treatment decisions [1478-1480].

It remains challenging, however, to evaluate whether the decision-making process can be viewed as successful; that is, whether the choice of treatment best reflects the patient's preferences and expectations [1481, 1482]. According to Decision Justification Theory (DJT), it is the more specific information on which treatment experiences lead to regret that decision regret needs to be better understood and to minimise it in future patients [1483]. Maguire *et al.*, found that about 25% of men with PCa undergoing either single or combined modality treatments report experiencing worse side effects than expected [1484]. Schroeck *et al.*, found urinary incontinence most strongly correlated with regret after prostatectomy [1485].

Unmet expectations are comparable among the treatment groups, except for fatigue. Fatigue is less frequently reported as worse than expected by patients who received BT when compared to patients who received RP or EBRT. This could be explained by the less invasive treatment course of BT in comparison to EBRT with or without ADT and RP [1486]. Unmet expectations were more frequently reported by patients with positive surgical margins following surgery; having had a passive role in the decision-making process; and who had higher scores on the decisional conflict scale (i.e. more uncertainty about the treatment decision). Interestingly, positive surgical margins are not directly associated with an increased risk of PC-related mortality [1064]. Active participation and support in the process of forming a preference increases the chance of choosing a treatment that is in line with patients' expectations [1480, 1487-1489].

While it may seem desirable to tailor the patients' role in decision-making to their initial preference, and particularly to a preference for deferring to the advice of the clinician, this does not result in less decisional conflict or regret. Increasing patients knowledge regardless of initial preference may actually be preferable [1485].

8.3.2.4 *Decision aids in prostate cancer*

Shared decision-making can increase patients' comfort when confronted with management decisions but has been shown to improve health outcome [1490] and more training seems needed for health care professionals guiding patients [1491]. Patient education decreased PSA testing [1492] and increased adherence to active surveillance protocols [1493, 1494]. Autonomous active decision-making by patients was associated with less regret after prostatectomy regardless of the method chosen and decision aids reduce decisional conflict [1495]. Still, guidance is needed to optimise patients' understanding of the options [1496]. Patients prioritised effectiveness and pain control over mode of administration and risk of fatigue when confronted with treatment choice in metastasised PCa [1497]. When implementing decision aids clinical validity and utility should be carefully evaluated and distinguished [1498]. A decision aid should educate as well as promote shared decision-making to optimise efficacy [1499] and pay attention to communicative aspects [1500].

8.3.2.5 *Guidelines for quality of life in men undergoing systemic treatments*

Recommendations	Strength rating
Offer men on androgen deprivation therapy (ADT), 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise men on ADT to maintain a healthy weight and diet, to stop smoking, reduce alcohol to ≤ 2 units daily and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer men with T1–T3 disease specialist nurse-led, multi-disciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support and positive lifestyle changes after any radical treatment.	Strong
Offer men starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Offer anti-resorptive therapy to men on long term ADT with either a BMD T-score of < -2.5 or with an additional clinical risk factor for fracture or annual bone loss on ADT is confirmed to exceed 5%.	Strong

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10. CONFLICT OF INTEREST

All members of the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/prostate-cancer/.

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1. INTRODUCTION

1.1 Aim

This guideline plays an important role in the process of consolidation and improvement of care for patients with pelvic pain and associated lower abdominal pain. From both literature and daily practice it has become clear that lower abdominal and pelvic pain are areas still under development. This guideline has been recognised as a cornerstone for important developments that have taken place in the past ten years.

This guideline aims to expand the awareness of caregivers in the field of abdominal and pelvic pain and to assist those who treat patients with abdominal and pelvic pain in their daily practice. The guideline is a useful instrument not only for urologists, but also for gynaecologists, surgeons, physiotherapists, psychologists and pain doctors.

It must be emphasised that guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

Structure and scope

The panel wishes to take advantage of modern methods of delivering guideline information to clinicians dealing with these patients. In 2016, a stepped information structure was made, in alignment with stepped care protocols, using new digital information sources like websites and apps to aid this process. Furthermore, the guideline was changed according to the template used in all other non-oncology guidelines of the EAU. It was recognised that structuring a guideline on chronic pain is quite different from structuring one on another subject. A multi-disciplinary approach is of utmost importance and demands a broad view. In 2016, the guideline was rewritten to be centred around pain instead of being organ-centred. It is partly theoretical to show the importance of using this pain-centred approach. The biggest part, however, deals with the practical approach to diagnostics, treatment and management of patients with abdominal and pelvic pain.

1.2 Publication history

The EAU Guidelines on Chronic Pelvic Pain were first published in 2003 [1] which formed the basis of a scientific publication in European Urology in 2004 [2]. Also, in the 2003 edition the concept of Chronic Pelvic Pain Syndromes (CPPS) was introduced, which is now referred to as “pain as a disease process”. Partial updates of the Chronic Pelvic Pain Guidelines were published in 2008 and formed the basis for another scientific publication in European Urology in the year 2010 [3, 4]. Two chapters were added at that time: Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 7 ‘Sexological aspects of chronic pelvic pain’. In the 2014 edition minor revisions were made in Chapter 5 ‘Gastrointestinal aspects of chronic pelvic pain’ and Chapter 8 ‘Psychological aspects of chronic pelvic pain’.

For the 2015 edition the panel critically reviewed the sub-chapter on chronic primary bladder pain syndrome (BPS) which is now a comprehensive part of the guideline. The fact that this part was so extensive shows that the roots of talking about abdominal pain and pelvic pain lies in the bladder, where Interstitial Cystitis was one of the first subjects addressed talking about pain in urology. The panel has illustrated this in the publication in European Urology in 2013 [5].

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. This reference document follows the updating cycle of the underlying large texts.

All available material can be viewed at the EAU website. The EAU website also includes a selection of EAU Guideline articles as well as translations produced by national urological associations: uroweb.org/guideline/chronicpelvicpain/.

1.4 Panel composition

The panel of experts responsible for this guideline include five urologists, (one of whom has a sub-specialisation in neuro-urology and one is a sexologist), three consultants in pain medicine, a uro-gynaecologist, a psychologist, a gastroenterologist, a pelvic physiotherapist, health scientist and (clinical) epidemiologist and two patient advocates.

1.5 Terminology

Definitions of chronic pelvic pain terminology

Classification

Much debate over the classification of chronic pelvic pain has occurred, is ongoing and will continue in the future. Classification involves three aspects of defining a condition: phenotyping, terminology and taxonomy.

Phenotyping

Phenotyping is describing the condition. For example, chronic bladder pain may be associated with the presence of Hunner's lesions and glomerulation on cystoscopy, whereas other bladder pain conditions may have a normal appearance on cystoscopy. These are two different phenotypes. The same is true for irritable bowel syndrome (IBS), which may be sub-divided into that associated primarily with diarrhoea or that with constipation. Phenotyping is based upon mechanisms when they are known (e.g., infection, ischaemic, auto-immune, or neuropathic). In the absence of well-defined mechanisms, describing the condition by its symptoms, signs and, where possible, by investigations, has been demonstrated to have clinical and research validity in many situations. When pain is the main symptom and pain as a disease process is considered the cause, the condition is often referred to as a pain syndrome - a well-defined collection of symptoms, signs and investigation results associated with pain mechanisms and pain perception as the primary complaint. The World Health Organization (WHO) International Classification of Diseases 11th Revision (ICD-11) uses the term Chronic Primary Pain to distinguish these conditions from pain associated with another diagnosis that they refer to as Chronic Secondary Pain (see below).

Terminology

Terminology is the word(s) that are used within classification, both to name the phenotype and within the definition of the phenotype. Examples of names for phenotypes associated with the bladder include interstitial cystitis, painful bladder syndrome or BPS. The EAU, the International Society for the study of BPS (known as ESSIC), the International Association for the Study of Pain (IASP) and several other groups have preferred the term BPS. In the pain syndromes, the role of the nervous system in generating the sensations is thought to be pivotal, but the term syndrome is also comprehensive and takes into account the emotional, cognitive, behavioural, sexual and functional consequences of the chronic pain.

When defining the phenotype, the terminology used in that definition must also be clear and if necessary, defined. One of the most important guiding principles is that spurious terminology should be avoided. Terms that end in "itis" should particularly be avoided, unless infection and or inflammation is proven and considered to be the cause of the pain [6]. It must be appreciated that end-organ inflammation may be secondary and neurogenic in origin and not a primary cause of the pain.

Taxonomy

Taxonomy places the phenotypes into a relationship hierarchy. The EAU approach sub-divides chronic pelvic pain into conditions that are pain syndromes with no obvious diagnosis, chronic primary pelvic pain syndromes (CPPPS) (consistent with ICD-11 Chronic Primary Pain) and those that are non-pain syndromes. The latter are conditions that have well-recognised pathology (e.g., infection, neuropathy or inflammation), whereas the former syndromes do not, and pain as a disease process is the mechanism. Other terms for the non-pain syndromes include "classical conditions", "well-defined conditions" and "confusable diseases" and the ICD-11 Chronic Secondary Pain. Although the EAU approach deals primarily with urological conditions, this approach to classification can be applied to all conditions associated with pain perception within the pelvis; the classification has been developed to include non-urological pain and was accepted by the IASP for publication in January 2012.

Classification of chronic pelvic pain

Importance of classification

It should be obvious to all that a condition cannot be treated unless it is defined. However, the reasons for classifying chronic pelvic pain go far beyond that.

Clues to the mechanism

As a result of systematic phenotypic and taxonomic classifications, similarities and differences between conditions become clear. Drawing comparisons between the phenotypes of different disorders allows comparison between disorders such as bladder and bowel pain syndromes, thus facilitating research and treatment.

Guidelines for best treatment options
As conditions become better defined, more specific treatment approaches can be adopted. In particular, there will be a move away from treatments based upon spurious terms (e.g., antibiotics and non-steroidal antiinflammatory drugs for the "-itis" conditions). Generic treatments aimed at groups of conditions will be more commonplace and based upon research evidence.

Research platform
Only by clearly defining the phenotype being investigated can research be valued or applied to the clinical situation.

Patient needs
A diagnosis, or name, for a set of symptoms can provide patients with a sense of being understood, as well as hope for relief. It may therefore help in acceptance of the problem as chronic, resolution of unfounded fears about its implications (if not life-threatening), and engagement in therapeutic endeavours, as well as assists in self-management. However, it may lead to accessing information of variable quality associated with the diagnosis or name, and the possibility of generating new concerns about long-term consequences or about the appropriateness of treatment.

IASP definitions
Sub-dividing pain syndromes
There is much debate on the sub-divisions of the pain syndromes within the hierarchical taxonomy. The EAU has led the way in this regard and the guiding principles are as follows [2]:

1. The pain syndromes are defined by a process of exclusion. In particular, there should be no evidence of infection or inflammation. Investigations by end-organ specialists should therefore be aimed at obtaining a differential diagnosis; repeated, unnecessary investigations are detrimental in the management of chronic pain syndromes.
2. A sub-division phenotype should only be used if there is adequate evidence to support its use. For instance, in non-specific, poorly localised pelvic pain without obvious pathology, only the term chronic primary pelvic pain syndrome (CPPPS) should be used. If the pain can be localised to an organ, then a more specific term, such as rectal pain syndrome, may be used, also potentially with the term primary added. If the pain is localised to multiple organs, then the syndrome is a regional pain syndrome and the term CPPPS should once again be considered. As well as defining the patient by a specific end-organ phenotype, there are several other more general descriptors that need to be considered. These are primarily psychological (e.g., cognitive or emotional), sexual, behavioural and functional. Psychological and behavioural factors are well-established factors which relate to quality of life (QoL) issues and prognosis. A North American research program, the MAPP program (Multi-disciplinary Approach to the study of Chronic Pelvic Pain research) has been devised to investigate the importance of these factors and looks at all types of pelvic pain irrespective of the end-organ where the pain is perceived. It also looks at systemic disorder associations, such as the co-occurrence of fibromyalgia, facial pain, or auto-immune disorders.
3. In 2004 the panel introduced the concept of managing the polysymptomatic nature of CPPPS, since then others have developed their own schemes, such as Nickel's UPOINT [7], modified by Magri *et al*. [8]. In light of these and other publications, the symptom classification table has been updated (Table 1).

The debate in relation to sub-dividing the pain syndromes continues. As more information is collected suggesting that the central nervous system (CNS) is involved, and indeed may be the main cause of many CPPPS conditions (e.g., bladder, genitalia, colorectal or myofascial), therefore there is a general tendency to move away from end-organ nomenclature. Only time and good research will determine whether this is appropriate. To enable such research, it is essential to have a framework of classification within which to work. Any hierarchical taxonomy must be flexible to allow change.

ICD classification: purpose and uses
The International Classification of Diseases is the foundation for the identification of health trends and statistics globally, and the international standard for reporting diseases and health conditions. It is the diagnostic classification standard for all clinical and research purposes. It defines the universe of diseases, disorders, injuries and other related health conditions, listed in a comprehensive and hierarchical fashion [9]. The latest version, ICD-11, is available for member states to report with from January 2022.

The ICD-11 classification for the first time included chronic pain ("chronic pain is pain that persists or recurs for longer than three months") and divided the coding into Chronic Primary Pain ("chronic primary pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome") and a number of Chronic Secondary Pain conditions (related to cancer, post surgical, musculoskeletal, visceral, neuropathic, headache/orofacial, other).

The significance of the inclusion of Chronic Pain as a condition within the ICD-11 should not be underestimated. There are, however, unresolved issues regarding this classification, such as when a condition ends and pain persists, does that term Chronic Secondary Pain become Chronic Primary Pain? [10, 11]. Similarly, the contents of recent drafted national institute for health and care excellence (NICE) guidelines [12] (https://www.nice.org.uk/guidance/GID-NG10069/documents/draft-guideline), were found to be contentious as the guidelines considered all Chronic Primary Pain as being essentially the same and the 'biological' nature of the pain appeared to have been missed. Whereas in the final guidelines this may be corrected, it does illustrate the risk behind the term Chronic Primary Pain.

The panel will change the EAU terminology previously used in the Guidelines to show conformity with ICD 11 definitions. This will include changing terminology used in originally cited works.

The classification has been set up according to the axis system used by IASP.

Table 1: EAU Classification of Chronic Pelvic Pain Syndromes

Axis I Region		Axis II System	Axis III End-organ as pain syndrome as identified from Hx, Ex and Ix		Axis IV Referral characteristics	Axis V Temporal characteristics	Axis VI Character	Axis VII Associated symptoms	Axis VIII Psychological symptoms
Chronic pelvic pain	Chronic secondary pelvic pain syndrome, formally known as specific disease associated pelvic pain OR Chronic primary pelvic pain syndrome, formally known as pelvic pain syndrome	Urological	Prostate		Suprapubic Inguinal Urethral Penile/clitoral Perineal Rectal Back Buttocks Thighs	ONSET Acute Chronic ONGOING Sporadic Cyclical Continuous TIME Filling Emptying Immediate post Late post TRIGGER Provoked Spontaneous	Aching Burning Stabbing Electric	UROLOGICAL Frequency Nocturia Hesitancy Dysfunctional flow Urgency Incontinence GYNAECOLOGICAL Menstrual Menopause GASTROINTESTINAL Constipation Diarrhoea Bloatedness Urgency Incontinence NEUROLOGICAL Dysaesthesia Hyperaesthesia Allodynia Hyperalgesia SEXUOLOGICAL Satisfaction Female dyspareunia Sexual avoidance Erectile dysfunction Medication MUSCLE Function impairment Fasciculation CUTANEOUS Trophic changes Sensory changes	ANXIETY About pain or putative cause of pain Catastrophic thinking about Pain DEPRESSION Attributed to pain or impact of pain Attributed to other causes Unattributed PTSD SYMPTOMS Re-experiencing Avoidance
				Bladder					
				Scrotal Testicular Epididymal					
				Penile Urethral					
				Post-vasectomy					
		Gynaecological	Vulvar Vestibular Clitoral						
			Endometriosis associated						
			CPPPS with cyclical exacerbations						
			Dysmenorrhoea						
		Gastrointestinal	Irritable bowel						
			Chronic anal						
			Intermittent chronic anal						
		Peripheral nerves	Pudendal pain syndrome						
		Sexological	Dyspareunia						
			Pelvic pain with sexual dysfunction						
		Psychological	Any pelvic organ						
		Musculo-skeletal	Pelvic floor muscle Abdominal muscle Spinal						
			Coccyx Hip muscle						

Hx = History; Ex = Examination; Ix = Investigation; PTSD = post-traumatic stress disorder.

Pain syndromes
The original EAU classification [2] was inspired by the IASP classification [13] and much work around what has become known as "pain as a disease" and its associated psychological, behavioural, sexual, social and organ function aspects. After ten years of work developing the initial ideas, an updated version was accepted by the IASP Council for publication in January 2012.

EAU Definition of chronic pelvic pain
Chronic pelvic pain is chronic or persistent pain perceived* in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract (LUT), sexual, bowel, pelvic floor or gynaecological dysfunction. [*Perceived indicates that the patient and clinician, to the best of their ability from the history, examination and investigations (where appropriate) have localised the pain as being discerned in a specified anatomical pelvic area.]

In the case of documented nociceptive pain that becomes chronic/persistent through time, pain must have been continuous or recurrent for at least three months (in accordance with ICD-11). For cyclical pain, a longer period of more than six months may be appropriate. Cyclical pain is included in the classification, particularly if there is evidence of central sensitisation and hence dysmenorrhoea (hormonally dependent) needs to be considered as a chronic pain syndrome, if it is persistent and associated with negative cognitive, behavioural, sexual, or emotional consequences.

Chronic pelvic pain may be sub-divided into conditions with well-defined classical pathology (such as infection or cancer) and those with no obvious pathology but still including biological mechanisms. For the purpose of the EAU's classification, the term "specific disease-associated pelvic pain" has been accepted for the former, and "chronic pelvic pain syndrome" for the latter. In the new ICD-11 these conditions have new names: the former will be called Chronic Secondary Pelvic Pain and the latter Chronic Primary Pelvic Pain.

The following classification only deals with Chronic Primary Pelvic Pain Syndromes.

EAU Definition of chronic primary pelvic pain syndrome
Chronic primary pelvic pain syndrome (CPPPS) is the occurrence of chronic pain when there is no proven infection or other obvious local pathology that may account for the pain. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of LUT, sexual, bowel or gynaecological dysfunction. Chronic Primary Pelvic Pain Syndrome is a subdivision of chronic pelvic pain. Throughout the text below in the 2021 update, CPPS is replaced with CPPPS if it is appropriate.

Further subdivision of chronic primary pelvic pain syndrome
Pain perception in CPPPS may be focused within a single organ, more than one pelvic organ and even associated with systemic symptoms such as chronic fatigue syndrome (CFS), fibromyalgia (FM) or Sjögren's syndrome. When the pain is localised to a single organ, some specialists may wish to consider using an end organ term such as BPS (Table 2), also using the term primary. The use of such a phrase with the terminology "syndrome" indicates that, although peripheral mechanisms may exist, CNS neuromodulation may be more important and systemic associations may occur. When the pain is localised to more than one organ site, the generic term CPPPS should be used. Many, including some of the panel members never sub-divide by anatomy and prefer to refer to patients with pain perceived within the pelvis, and no specific disease process, as suffering from CPPPS, sub-divided by psychological and functional symptoms.

Psychological considerations for classification
Many CPPPSs are associated with a range of concurrent negative psychological, behavioural and sexual consequences that must be described and assessed. Examples that need to be considered are depression, anxiety, fears about pain or its implications, unhelpful coping strategies, and distress in relationships. Both anxiety and depression can be significant important concomitant symptoms that are relevant to pain, disability and poor QoL. Catastrophic interpretation of pain has been shown to be a particularly salient variable, predicting patients' report of pain, disability, and poor QoL, over and above psychosocial variables such as depression or behavioural factors such as self-reported sexual dysfunction. Many of these biopsychosocial consequences are common to other persistent pain problems but may show varying degrees of importance for any one individual suffering from CPPPS. In all patients with CPPPS, these consequences must be clearly described as part of the phenotype (where the term phenotype is used to indicate the observable characteristics of the syndrome) [14].

Functional considerations for classification

Functional disorders, for the purpose of this document, are pathologies that have arisen secondary to changes in the control mechanisms of an organ or system. That is, they are disorders characterised by disturbance of function. As an example, slow colonic transit is a functional disorder of the bowel - the normal function of the bowel is not occurring as a result of changes in the mechanisms that produce defecation, and therefore bowel control is altered. The term is not used in the sense of a psychiatric functional disorder. Many CPPPSs are associated with functional abnormalities at a local and even systemic level. These also need to be defined as a part of the phenotype.

Functional pain disorders may not include significant pathology in the organs that appear responsible for the primary symptoms, but they are associated with substantial neurobiological, physiological and sometimes anatomical changes in the CNS.

Multi-system sub-division

It is recognised that the end-organ where the pain is perceived may not be the centre of pain generation. This classification is based upon the most effective and accepted method of classifying and identifying different pain syndromes, that is, by site of presentation. It is argued that keeping the end-organ name in the classification is inappropriate because, in most cases, there are multi-systemic causes and effects, with the result that symptoms are perceived in several areas. This is an area in which discussions are ongoing, and despite there being strong arguments for both keeping and dispensing with end-organ classification, the panel have not taken the umbrella approach of referring to all pain perceived in the pelvis as CPPS, primary or secondary.

Dyspareunia

Dyspareunia is defined as pain perceived within the pelvis associated with penetrative sex. It tells us nothing about the mechanism and may be applied to women and men. It is usually applied to penile penetration, but is often associated with pain during insertion of any object. It may apply to anal as well as vaginal intercourse. It is classically sub-divided into superficial and deep.

Primary perineal pain syndrome

Primary perineal pain syndrome is a neuropathic-type pain that is perceived in the distribution area of the pudendal nerve, and may be associated with symptoms and signs of rectal, urinary tract or sexual dysfunction. There is no proven obvious pathology. It is often associated with negative cognitive, behavioural, sexual and emotional consequences, as well as with symptoms suggestive of LUT, sexual, bowel or gynaecological dysfunction. Primary perineal pain syndrome should be distinguished from pudendal neuralgia which is a specific disease associated with perineal pain that is caused by nerve damage.

Table 2: Chronic Primary Pelvic Pain Syndromes (the term primary can be included in any of the following)

Urological Pain Syndromes	
Primary prostate pain syndrome	Primary prostate pain syndrome (PPPS) is the occurrence of persistent or recurrent episodic pain (which is convincingly reproduced by prostate palpation). There is no proven infection or other obvious local pathology. Primary prostate pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. The term “chronic prostatitis” continues to be equated with that of PPPS. In the authors’ and others’ opinion, this is an inappropriate term, although it is recognised that it has a long history of use. The National Institutes of Health (NIH) consensus [15] includes infection (types I and II), which the authors feel should not be considered under PPPS, but as specific disease-associated pelvic pain. The term prostadynia has also been used in the past but is no longer recommended by the expert panel. Please note that some of the authors of the IASP document disagree with this term and suggest that CPPPS of the male is used instead of PPPS, which has been agreed by the majority.

Primary bladder pain syndrome	Primary bladder pain syndrome is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency. There is no proven infection or other obvious local pathology. Primary bladder pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. PBPS is believed to represent a heterogeneous spectrum of disorders. There may be specific types of inflammation as a feature in subsets of patients. Localisation of the pain can be difficult by examination, and consequently, another localising symptom is required. Cystoscopy with hydrodistension and biopsy may be indicated to define phenotypes. Recently, ESSIC has suggested a standardised scheme of sub-classifications [16] to acknowledge differences and make it easier to compare various studies. Other terms that have been used include “interstitial cystitis”, “painful bladder syndrome”, and “PBS/IC” or “BPS/IC”. These terms are no longer recommended.
Primary scrotal pain syndrome	Primary scrotal pain syndrome is the occurrence of persistent or recurrent episodic pain localised to the scrotum or the structure within it and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Primary scrotal pain syndrome is a generic term and is used when the site of the pain is not clearly testicular or epididymal. The pain is not in the skin of the scrotum as such, but perceived within its contents, in a similar way to idiopathic chest pain.
Primary testicular pain syndrome	Primary testicular pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the testes, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary testicular pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included orchitis, orchialgia and orchiodynia. These terms are no longer recommended
Primary epididymal pain syndrome	Primary epididymal pain syndrome is the occurrence of persistent or recurrent episodic pain perceived in the epididymis, and may be associated with symptoms suggestive of lower urinary tract or sexual dysfunction. There is no proven infection or other obvious local pathology. Primary epididymal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences.
Primary penile pain syndrome	Primary penile pain syndrome is the occurrence of pain within the penis that is not primarily in the urethra, in the absence of proven infection or other obvious local pathology. Primary penile pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction.
Primary urethral pain syndrome	Primary urethral pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the urethra, in the absence of proven infection or other obvious local pathology. Primary urethral pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Primary urethral pain syndrome may occur in men and women.
Post-vasectomy scrotal pain syndrome	Post-vasectomy scrotal pain syndrome is a scrotal pain syndrome that follows vasectomy. Post-vasectomy scrotal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract and sexual dysfunction. Post-vasectomy pain may be as frequent as 1% following vasectomy, possibly more frequent. The mechanisms are poorly understood and for that reason it is considered by some a special form of primary scrotal pain syndrome.

Primary Gynaecological Pain Syndromes: external genitalia	
Primary vulvar pain syndrome	Primary vulvar pain syndrome is the occurrence of persistent or recurrent episodic vulvar pain. There is no proven infection or other local obvious pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Although pain perceived in the vulva was included under sexual disorders in the DSM-IV-R manual for classifying psychiatric disorders, there is no scientific basis for this classification, and pain perceived in the vulva is best understood as a pain problem that usually has psychological consequences. There is no evidence for its classification as a psychiatric disorder. The International Society for the Study of Vulvovaginal Disease (ISSVD) has used the term vulvodynia, where we use the term primary vulvar pain syndrome. According to the ISSVD, vulvodynia is vulvar pain that is not accounted for by any physical findings. The ISSVD has defined vulvodynia as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder". If physical findings are present, the patient is said to have vulvar pain due to a specified cause. The ISSVD has sub-divided vulvodynia based on pain location and temporal characteristics of the pain (e.g. provoked or unprovoked). The following definitions are based on that approach.
Primary generalised vulvar pain syndrome	Primary generalised vulvar pain syndrome refers to a vulvar pain syndrome in which the pain/burning cannot be consistently and precisely localised by point-pressure mapping via probing with a cotton-tipped applicator or similar instrument. Rather, the pain is diffuse and affects all parts of the vulva. The vulvar vestibule (the part that lies between the labia minora into which the urethral meatus and vaginal introitus open) may be involved but the discomfort is not limited to the vestibule. This pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences. Previous terms have included "dysesthetic vulvodynia" and "essential vulvodynia", but these are no longer recommended.
Primary localised vulvar pain syndrome	Primary localised vulvar pain syndrome refers to pain that can be consistently and precisely localised by point-pressure mapping to one or more portions of the vulva. Clinically, the pain usually occurs as a result of provocation (touch, pressure or friction). Primary localised vulvar pain syndrome can be sub-divided into primary vestibular pain syndrome and primary clitoral pain syndrome.
Primary vestibular pain syndrome	Primary vestibular pain syndrome refers to pain that can be localised by point-pressure mapping to the vestibule or is well perceived in the area of the vestibule.
Primary clitoral pain syndrome	Primary clitoral pain syndrome refers to pain that can be localised by point-pressure mapping to the clitoris or is well-perceived in the area of the clitoris.
Gynaecological system: internal pelvic pain syndromes	
Endometriosis-associated pain syndrome	Endometriosis-associated pain syndrome is chronic or recurrent pelvic pain in patients with laparoscopically confirmed endometriosis, and the term is used when the symptoms persist despite adequate endometriosis treatment. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. Many patients have pain above and beyond the endometriotic lesions; this term is used to cover that group of patients. Endometriosis may be an incidental finding, is not always painful, and the degree of disease seen laparoscopically does not correlate with severity of symptoms. As with other patients, they often have more than one end-organ involved. It has been suggested that this phenotype should be removed from the classification because the endometriosis may be irrelevant.
Chronic primary pelvic pain syndrome with cyclical exacerbations	Chronic primary pelvic pain syndrome with cyclical exacerbations covers the non-gynaecological organ pain that frequently shows cyclical exacerbations (e.g., IBS or PBPS) as well as pain similar to that associated with endometriosis/adenomyosis but where no pathology is identified. This condition is different from dysmenorrhoea, in which pain is only present with menstruation.
Primary dysmenorrhoea	Primary dysmenorrhoea is pain with menstruation that is not associated with well-defined pathology. Dysmenorrhoea needs to be considered as a chronic primary pain syndrome if it is persistent and associated with negative cognitive, behavioural, sexual or emotional consequences.

Gastrointestinal Pelvic Pain Syndromes	
Irritable bowel syndrome	Irritable bowel syndrome is the occurrence of chronic or recurrent episodic pain perceived in the bowel, in the absence of proven infection or other obvious local pathology. Bowel dysfunction is frequent. Irritable bowel syndrome is often associated with worry and pre-occupation about bowel function, and negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract or gynaecological dysfunction. The above classification is based upon the Rome III Criteria [17]: three months of continuous or recurring symptoms of abdominal pain or irritation that may be relieved with a bowel movement, may be coupled with a change in frequency, or may be related to a change in stool consistency. Two or more of the following are present at least 25% of the time: change in stool frequency (> three bowel movements per day or < three per week); noticeable difference in stool form (hard, loose, watery or poorly formed stools); passage of mucus in stools; bloating or feeling of abdominal distension; or altered stool passage (e.g., sensation of incomplete evacuation, straining, or urgency). Extra-intestinal symptoms include: nausea, fatigue, full sensation after even a small meal, and vomiting.
Chronic primary anal pain syndrome	Chronic primary anal pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the anus, in the absence of proven infection or other obvious local pathology. Chronic primary anal pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction.
Intermittent chronic primary anal pain syndrome	Intermittent chronic primary anal pain syndrome refers to severe, brief, episodic pain that seems to arise in the rectum or anal canal and occurs at irregular intervals. This is unrelated to the need to or the process of defecation. It may be considered a sub-group of the chronic primary anal pain syndromes. It was previously known as “proctalgia fugax” but this term is no longer recommended.
Musculoskeletal System	
Primary pelvic floor muscle pain syndrome	Primary pelvic floor muscle pain syndrome is the occurrence of persistent or recurrent episodic pelvic floor pain. There is no proven well-defined local pathology. It is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. This syndrome may be associated with over-activity of, or trigger points within, the pelvic floor muscles. Trigger points may also be found in several muscles, such as the abdominal, thigh and paraspinal muscles and even those not directly related to the pelvis.
Primary coccyx pain syndrome	Primary coccyx pain syndrome is the occurrence of chronic or recurrent episodic pain perceived in the region of the coccyx, in the absence of proven infection or other obvious local pathology. Primary coccyx pain syndrome is often associated with negative cognitive, behavioural, sexual or emotional consequences, as well as with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction. The term “coccydynia” was used but is no longer recommended.
Chronic Pain Post-Surgery	
Chronic post-surgical pain syndrome	The definition of chronic post-surgical pain is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least three months after the surgery. There is a separate category for this in the ICD11 classification.

2. METHODOLOGY

2.1 Methods

For each recommendation within the guidelines there is an accompanying strength rating form, the basis of which is a modified GRADE methodology [18]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [19];

2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related
4. factors);
5. the balance between desirable and undesirable outcomes;
6. the impact of patient values and preferences on the intervention;
7. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [18]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

The 2012 full text update was based on a systematic review (SR) of literature using the Embase and Medline databases, the Cochrane Central Register of controlled trials and the PsycINFO and Bandolier databases to identify the best evidence from randomised controlled trials (RCTs) (Level of Evidence 1 [LE: 1]) according to the rating schedule adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence. Where no LE: 1 literature could be identified the search was moved down to the next lower level on the rating scale.

Extensive use of free text ensured the sensitivity of the searches, resulting in a substantial body of literature to scan. Searches covered the period January 1995 to July 2011 and were restricted to English language publications. In 2017, a scoping search for the previous five years was performed and the guideline was updated accordingly.

In 2021, a new section was included on Post-Surgical Pain Syndrome. In addition, the classifications in the Guideline have been amended to reflect ICD-11 released by WHO. The latest version of ICD-11 will be available for member states to report with as from January 2022. For the 2022 print, a scoping search for the previous three years was performed and the guideline was updated accordingly.

2.2 Review

This document was subject to peer review prior to publication in 2021.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

3.1 Chronic visceral pain

Definition of pain

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP Taxonomy).

Introduction to chronic pelvic primary pain syndromes

Over the years much of the focus for CPPPS has been on peripheral-end-organ mechanisms, such as inflammatory or infective conditions. However, both animal and clinical research have indicated that many of the mechanisms for the CPPPSs are based within the CNS. Although a peripheral stimulus such as infection may initiate the start of a CPPPS condition, the condition may become self-perpetuating as a result of CNS modulation. As well as pain, these central mechanisms are associated with several other sensory, functional, behavioural and psychological phenomena. It is this collection of phenomena that forms the basis of the pain syndrome diagnosis and each individual phenomenon needs to be addressed in its own right through multi-specialty and multi-disciplinary care. Although ongoing peripheral organ pathology can produce persistent and chronic pain, the main focus of these guidelines is on CPPPSs in which no peripheral ongoing pathology (such as infection or neoplastic disease) is detected. The main exception is when pain is due to peripheral nerve damage.

3.1.1 ***Incidence***

No adequate data on incidence were found.

3.1.2 ***Prevalence***

Across the world [20] chronic pain is prevalent, seriously affecting the quality of people's social, family, and working lives, with differences between countries attributable to multiple causes, including study methodology. A UK study found a prevalence of chronic pelvic pain of 14.8% in women over 25 years [21].

3.1.3 ***Influence on Quality of Life***

Assessing QoL in pelvic pain patients is challenging due to the complex pathology, the multi-faceted nature of the complaints and the overlap between the different pelvic pain syndromes [22, 23]. Pelvic pain syndromes have an impact in terms of QoL [24, 25], depression, anxiety, impaired emotional functioning, insomnia and fatigue [24, 26]. If these aspects are identified and targeted early in the diagnostic process, the associated pain symptoms may also improve. Addressing comorbidities will help in further improving QoL [27]. Quality of life assessment is therefore important in patients with pelvic pain and should include physical, psychosocial and emotional tools, using standardised instruments where possible [25]. Chronic pain is, in many countries, the leading cause of years lost to disability [20], although these figures are dominated by musculoskeletal pain and headache. Chronic pain is often associated with depression and other psychological problems; with loss or reduction of work and of ability to carry out domestic tasks; and, with substantial use of healthcare, often with disappointing outcomes.

3.1.4 ***Costs***

No adequate data on costs were found.

3.1.5 ***Risk Factors and underlying causes***

3.1.5.1 Risk factors

Risk factors include many different factors from various areas, including genetic, psychological state, recurrent physical trauma and endocrine factors.

The endocrine system is involved in visceral function. Significant life events, and in particular, early life events may alter the development of the hypothalamic-pituitary-adrenal axis and the chemicals released. Increased vulnerability to stress is thought to be partly due to increased corticotrophin-releasing hormone (CRH) gene expression. Up-regulation of CRH has been implicated in several pain states such as rectal hypersensitivity to rectal distension. This model suggests an action of CRH on mast cells. A range of stress-related illnesses have been suggested, e.g., IBS and BPS. There is evidence accumulating to suggest that the sex hormones also modulate both nociception and pain perception. Stress can also produce long-term biological changes which may form the relation between chronic pain syndromes and significant early life and adverse life events [28]. Asking the patient about these events is important as they have an effect on a patient's psychological wellbeing [29, 30].

Genetics also play a role in assessing the risk of developing chronic pain. An individual who has one chronic pain syndrome is more likely to develop another. Family clusters of pain conditions are also observed and animals can be bred to be more prone to apparent chronic pain state. A range of genetic variations have been described that may explain the pain in certain cases; many of these are to do with subtle changes in transmitters and their receptors. However, the picture is more complicated in that developmental, environmental and social factors also influence the situation. Evidence that PBPS may have a genetic component has been presented in several identical twin studies, but genetics may contribute to less than one third of total variation in susceptibility to PBPS [31, 32].

Studies about integrating the psychological factors of CPPPSs are few but the quality is high. Psychological factors are consistently found to be relevant in the maintenance of persistent pelvic and urogenital pain [33]. Beliefs about pain contribute to the experience of pain [34] and symptom-related anxiety and central pain amplification may be measurably linked, as in IBS [35], and catastrophic thinking about pain and perceived stress predict worsening of urological chronic pain over a year [33, 36]. Central sensitisation has been demonstrated in symptomatic endometriosis [37] and central changes are evident in association with dysmenorrhoea and increasingly recognised as a risk for female pelvic pain [38]. The various mechanisms of CNS facilitation, amplification and failure of inhibition mean that there is no simple relationship between physical findings, pain experience and resulting distress and restriction of activities. Division of aetiology into organic vs. psychogenic is unscientific. Diagnoses that assign women's pain to psychological origins due to scepticism about the reality or severity of their pain [39, 40] undermines any therapeutic relationship [41]. Pelvic

pain and distress may be related [42] in both men and women [43]; as are painful bladder and distress [36]. In a large population based study of men, CPPPS was associated with prior anxiety disorder [44]. The only SR [45] of risk factors for chronic non-cyclical pelvic pain in women included, as well as medical variables: sexual or physical abuse (Odds Ratio (OR): 1.51-3.49); psychological problems such as anxiety (OR: 2.28; 95% Confidence Interval (CI): 1.41-3.70) and depression (OR: 2.69; 95% CI: 1.86-3.88); multiple somatic problems (OR: 4.83; 95% CI: 2.50-9.33 and OR: 8.01; 95% CI: 5.16-12.44).

Many studies have reported high rates of childhood sexual abuse in adults with persistent pain, particularly in women with pelvic pain [46]. It is hard to establish a causal role for sexual abuse or trauma history, anxiety or depression in women with CPPPS [47, 48], as the attribution of current pain to past sexual or physical abuse is associated both with current depression [49] and with current overall physical health [50]. There is some evidence for a specific relationship between rape and CPPPS (and with fibromyalgia and functional gastrointestinal disorders) [51]; and, recent sexual assault may prompt presentation of pelvic pain [46, 52]. Few studies have been found of sexual or physical abuse in childhood and pelvic pain in men, although it has known adverse effects on health [51], but men who reported having experienced sexual, physical or emotional abuse had increased odds (3.3 vs. 1.7) for symptoms suggestive of CPPPS [53]. Both sexes should be screened for sexual abuse when presenting with symptoms suggestive of CPPPS, and clinicians should inquire about pelvic pain in patients who have experienced abuse [53].

3.1.5.2 Underlying causes

The mechanisms that serve as an underlying cause for chronic pelvic pain are:

1. Ongoing acute pain mechanisms [54] (such as those associated with inflammation or infection), which may involve somatic or visceral tissue.
2. Chronic pain mechanisms, which especially involve the CNS [6].
3. Emotional, cognitive, behavioural and sexual responses and mechanisms [55-57].

Symptoms and signs of neuropathic pain appear to be common in CPPPS patients and assessment of neuropathic pain should be considered in that group of patients. The presence or absence of endometriosis does not seem to change this [58].

Chronic pain mechanisms may include altered resting state neuromotor connectivity, for instance in men with chronic prostatitis/CPPPS [59].

Table 3 illustrates some of the differences between the somatic and visceral pain mechanisms. These underlie some of the mechanisms that may produce the classical features of visceral pain; in particular, referred pain and hyperalgesia.

Table 3: Comparison between visceral and somatic pain

	Visceral pain	Somatic pain
Effective painful stimuli	Stretching and distension, producing poorly localised pain.	Mechanical, thermal, chemical and electrical stimuli, producing well localised pain.
Summation	Widespread stimulation produces significantly magnified pain.	Widespread stimulation produces a modest increase in pain.
Autonomic involvement	Autonomic features (e.g., nausea and sweating) frequently present.	Autonomic features less frequent.
Referred pain	Pain perceived at a site distant to the cause of the pain is common.	Pain is relatively well localised and well recognised.
Referred hyperalgesia	Referred cutaneous and muscle hyperalgesia is common, as is involvement of other visceral organs.	Hyperalgesia tends to be localised.
Innervation	Low density, unmyelinated C fibres and thinly myelinated A∂ fibres.	Dense innervation with a wide range of nerve fibres.
Primary afferent physiology	Intensity coding. As stimulation increases, afferent firing increases with an increase in sensation and ultimately pain.	Two fibre coding. Separate fibres for pain and normal sensation.
Silent afferents	50-90% of visceral afferents are silent until the time they are switched on.	These fibres are very important in the central sensitisation process. Silent afferents present, but form a lower percentage.
Central mechanisms	Play an important part in the hyperalgesia, viscero-visceral, viscero-muscular and musculo-visceral hyperalgesia.	Sensations not normally perceived become perceived and non-noxious sensations become painful. Responsible for the allodynia and hyperalgesia of chronic somatic pain.
Abnormalities of function	Central mechanisms associated with visceral pain may be responsible for organ dysfunction.	Somatic pain associated with somatic dysfunction, e.g., muscle spasm.
Central pathways and representation	As well as classical pathways, there is evidence for a separate dorsal horn pathway and central representation.	Classical pain pathways.

Ongoing peripheral pain mechanisms in visceral pain

In most cases of chronic pelvic pain, ongoing tissue trauma, inflammation or infection is absent [60, 61]. However, conditions that produce recurrent trauma, infection or ongoing inflammation may result in chronic pelvic pain in a small proportion of cases. For example, out of a large cohort with acute bacterial prostatitis, 10.5% ended up with a state of CPPPS [62]. It is for this reason that the early stages of assessment include looking for these pathologies [16]. Once excluded, ongoing investigations for these causes are rarely helpful and indeed may be detrimental.

When acute pain mechanisms are activated by a nociceptive event, as well as direct activation of the peripheral nociceptor transducers, sensitisation of those transducers may also occur; therefore, magnifying the afferent signalling. Afferents that are not normally active may also become activated by the change, that is, there may be activation of the so-called silent afferents. Although these are mechanisms of acute pain, the increased afferent signalling is often a trigger for the chronic pain mechanisms that maintain the perception of pain in the absence of ongoing peripheral pathology (see below) [63].

There are a number of mechanisms by which the peripheral transducers may exhibit an increase in sensibility:

1. Modification of the peripheral tissue, which may result in the transducers being more exposed to peripheral stimulation.
2. There may be an increase in the chemicals that stimulate the receptors of the transducers [64].
3. There are many modifications in the receptors that result in them being more sensitive.

In general, the effect of 1 and 2 above is to lower the threshold and the effect of 3 above is to increase responsiveness to external stimuli. Some of the chemicals responsible for the above changes may be released from those cells associated with inflammation, but the peripheral nervous system may also release chemicals in the positive and inhibitory loops [65, 66].

Central sensitisation as a mechanism in visceral pain

It is important to appreciate that nociception is the process of transmitting information to centres involved in perception of a stimulus that has the potential to cause tissue damage. Pain is far more complex and involves activation of the nociceptive pathways but also the emotional response. The brain may affect the modulation of pain pathways at the spinal cord level.

Neuronal sensitisation is responsible for a decrease in threshold and an increase in response duration and magnitude of dorsal horn neurons. It is associated with an expansion of the receptive field. As a result, sensitisation increases signalling to the CNS and amplifies what we perceive from a peripheral stimulus. For example, for cutaneous stimuli, light touch would not normally produce pain, however, when central sensitisation is present, light touch may be perceived as painful (allodynia). In visceral hyperalgesia (so called because the afferents are primarily small fibres), visceral stimuli that are normally sub-threshold and not usually perceived, may be perceived. For instance, with central sensitisation, stimuli that are normally sub-threshold may result in a sensation of fullness and a need to void or to defecate. Non-noxious stimuli may be interpreted as pain and stimuli that are normally noxious may be magnified (true hyperalgesia) with an increased perception of pain. As a consequence, one can see that many of the symptoms of PBPS and IBS may be explained by central sensitisation. A similar explanation exists for the muscle pain in FM.

It is now well accepted that there are both descending pain-inhibitory and descending pain-facilitatory pathways that originate from the brain [67]. Several neurotransmitters and neuromodulators are involved in descending pain-inhibitory pathways. The main ones are the opioids, 5-hydroxytryptamine and noradrenaline.

The autonomic nervous system also plays a role in sensitisation. There is good evidence that damaged afferent fibres may develop a sensitivity to sympathetic stimulation, both at the site of injury and more centrally, particularly in the dorsal horns. In visceral pain, the efferent output of the CNS may be influenced by central changes (again, those changes may be throughout the neuraxis), and such modification of the efferent message may produce significant end-organ dysfunction. These functional abnormalities can have a significant effect on QoL and must be managed as appropriate.

Psychological mechanisms in visceral pain

Psychological processes of emotions, thought and behaviour involve networks rather than distinct centres. Some of these processes are sophisticated and others fundamental in evolutionary terms, and their interaction with pain processing is complex.

Various psychological processes affect pain neuromodulation at a higher level. Inhibiting or facilitating both the strength of the nociceptive signal reaching the consciousness and appraisal and interpretation of that signal, will also modulate the response to the nociceptive message and hence the pain experience. Further, descending pathways represent cognitive, emotional and behavioural states at spinal and peripheral levels. The psychological modulation of visceral pain probably involves multiple pathways: for instance, mood and attentional focus probably act through different areas of the brain when involved in reducing pain [68].

This psychological modulation may act to reduce nociception within a rapid time frame but may also result in long-term vulnerability to chronic visceral pain, through long-term potentiation. This involvement of higher centre learning may be at both a conscious and subconscious level, and is clearly significant in the supratentorial neuroprocessing of nociception and pain. Long-term potentiation [69] may occur at any level within the nervous system, so that pathways for specific or combinations of stimuli may become established, resulting in an individual being vulnerable to feeling pain from sensations that would not normally be experienced as painful.

An important review [28] of chronic pelvic pain in women dismantled the notion that women without relevant physical findings differ in psychological characteristics from women with relevant physical findings. Women with pelvic pain often have other non-pain somatic symptoms and current or lifetime anxiety and depression disorder [21]; they may have a history of physical or sexual abuse in childhood; but this is of unclear significance. Studies should avoid interpreting the absence of physical findings as evidence for psychological originis of the complaint (‘psychosomatic’ or ‘somatoform’ disorders). Pain studies describe multiple processes

by which pain may spread across sites, or in time, including central sensitisation (see previous section), viscero-visceral cross sensitisation in relation to multiple pain sites [70], activation of the hypothalamic-pituitary axis and dysregulation of serotonergic pathways [71] that can render pain levels responsive to stress. Some pain problems which affect sexual activity are diagnosed as sexual problems (e.g., 'dyspareunia') when pain is the central problem and is not contingent on sexual activity alone [72]. Better integration of sexology and mainstream psychology for pelvic pain in both men and women is needed, building on a biopsychosocial formulation [73, 74].

The term psychosomatic symptoms can best be understood as multiple somatic symptoms not associated with, or indicative of, any serious disease process. Medical and surgical history may also be important [75].

Understanding the psychological components of pain

Psychological processes of emotions, thought and behaviour involve distributed networks, whose interactions with pain processing are complex, producing inhibition and facilitation of signal processing, appraisal, and response. Models that integrate psychological factors involved in maintaining persistent pelvic and urogenital pain with current neurobiological understanding of pain are few, but the quality is high (see Section 3.1.5.1).

There is no evidence that women with CPPPS without physical findings are primarily presenting a psychological problem [28]. Anxiety and post-traumatic stress symptoms are common in some women with CPPPS [40, 76] and with vulvar pain [77], and may account for substantial variance in health status, treatment use and treatment outcome; for instance, women's expectations about vulvar pain on penetration predicted pain, sexual function and sexual satisfaction [78]. Negative investigative findings do not necessarily resolve women's anxieties about the cause of pain [79, 80] and anxiety often focuses on what might be 'wrong'. Depression may be related to pain in various ways, as described above. Until measures are available that are adequately standardised in patients with pain, assessment of anxiety and distress requires questions about the patient's beliefs about the cause of pain, the hope that diagnosis will validate pain, the struggle with unpredictability, and the implications of pain for everyday life [81, 82]. Reference to the studies of the IMMPACT group [83] is recommended for guidance on outcome measures suitable for pain trials.

Stress can modify the nervous system to produce long-term biological changes. These structural changes may be responsible for significant early life and adverse life events which are associated later with chronic pain syndromes [30]. The patient should be asked about adverse life events that may produce these biological responses and affect general psychological well-being [30, 84].

3.1.5.3 Clinical paradigms in visceral pain

Referred pain

Referred pain is frequently observed and its identification is important for diagnosis and treatment. Referral is usually somatic to somatic, or visceral to somatic. However, there is no reason why pain cannot also be perceived within the area of an organ with the nociceptive signal having arisen from a somatic area. Referred pain may occur as a result of several mechanisms but the main theory is one of convergence-projection. In the convergence-projection theory, afferent fibres from the viscera and the somatic site of referred pain converge onto the same second order projection neurons. The higher centres receiving messages from these projection neurons are unable to separate the two possible sites from the origin of the nociceptive signal [63].

Hyperalgesia refers to an increased sensitivity to normally painful stimuli. In patients that have passed a renal stone, somatic muscle hyperalgesia is frequently present, even a year after expulsion of the stone. Pain to non-painful stimuli (allodynia) may also be present in certain individuals. Somatic tissue hyperaesthesia is associated with urinary and biliary colic, IBS, endometriosis, dysmenorrhoea, and recurrent bladder infections. Primary vulvar pain syndromes are examples of cutaneous allodynia that, in certain cases, may be associated with visceral pain syndromes, such as BPS. Referred pain with hyperalgesia is thought to be due to central sensitisation of the converging viscero-somatic neurons. Central sensitisation also stimulates efferent activity that could explain the trophic changes that are often found in the somatic tissues.

Musculo-skeletal system and pelvic pain

In the urogenital pain syndromes, muscle tenderness and trigger points may be implicated as a source of pain. Central mechanisms are of great importance in the pathogenesis of this muscle hyperalgesia. The muscles involved may be a part of the spinal, abdominal or pelvic complex of muscles. It is not unknown for adjacent muscles of the lower limbs and the thorax to become involved. Pain may be localised to the trigger points but it is more often associated with classical referral patterns. As well as trigger points, inflammation of the ligaments and tendons to the bones (enthesitis) and of the bursa (bursitis) may be found [85]. Certain postures affect the

different muscles in different ways, and as a consequence, may exacerbate or reduce the pain. Stress has been implicated as both an initiator of pelvic myalgia and as a maintenance factor. As a result, negative sexual encounters may also have a precipitating effect [28].

Visceral hyperalgesia

The increased perception of stimuli in the viscera is known as visceral hyperalgesia, and the underlying mechanisms are thought to be responsible for IBS, PBPS and dysmenorrhoea. The mechanisms involved are often acute afferent input (e.g., due to infection) followed by long-term central sensitisation. Viscero-visceral hyperalgesia is thought to be due to two or more organs with converging sensory projections and central sensitisation. For instance, overlap of bladder and uterine afferents or uterine and colon afferents.

3.2 Pelvic pain

*3.2.1 **Incidence***

No adequate data on incidence were found.

*3.2.2 **Prevalence***

3.2.2.1 Primary prostate pain syndrome

There is only limited information on the true prevalence of PPPS in the population. As a result of significant overlap of symptoms with other conditions (e.g., benign prostatic enlargement and PBPS), purely symptom based case definitions may not reflect the true prevalence of PPPS [86, 87]. In the literature, population-based prevalence of prostatitis symptoms ranges from 1-14.2% [88, 89]. The risk of prostatitis increases with age (men aged 50-59 years have a 3.1-fold greater risk than those aged 20-39 years).

3.2.2.2 Primary bladder pain syndrome

Reports of PBPS prevalence have varied greatly, along with the diagnostic criteria and populations studied. Recent reports range from 0.06-30% [90-99]. There is a female predominance of about 10:1 [96] but possibly no difference in race or ethnicity [86, 100, 101]. The relative proportions of Hunner's lesion and non-lesion disease are unclear. Incidence in studies has ranged from 5-50% [102-105]. There is increasing evidence that children under eighteen may also be affected, although prevalence figures are low; therefore, PBPS cannot be excluded on the basis of age [106].

3.2.2.3 Sexual pain syndrome

In the 1980s, an association between chronic pelvic pain and sexual dysfunction was postulated. In a review the relationship between Primary Prostate Pain Syndrome and health status, with influence on sexual activity, was addressed [107]. In a Chinese study of men with chronic pelvic pain, 1,768 males completed the questionnaires. The overall prevalence of sexual dysfunction was 49%. Erectile dysfunction (ED) is the most investigated sexual dysfunction in PPPS patients. The reported prevalence of ED ranges from 15.1-48%, varying with evaluation tools and populations [108, 109]. Erectile dysfunction was prevalent in 27.4% of Italian men aged 25-50 [110], 15.2% among Turkish men (significantly higher than in the control group) [111] and 43% among Finnish men with PPPS [112]. The prevalence of ED was found to be higher in young men with PPPS than in the general population. According to other studies, men with pelvic pain had a higher chance of suffering from ED [113]. A significant correlation between "chronic prostatitis", chronic pelvic pain symptoms (measured by NIH-CPSI) and ED (measured by International Index of Erectile Function [IIEF]) was confirmed [114], while other studies using the same questionnaires were not able to confirm such a correlation [74, 115]. Some studies also report ejaculatory dysfunction, mainly premature ejaculation [108, 109, 116, 117].

In community-based studies in the UK [118], New Zealand [119] and Australia [120], a substantially larger proportion of the women with chronic pelvic pain reported dyspareunia (varying between 29-42%) than women without chronic pelvic pain (varying between 11-14%). Only a few studies have investigated sexual problems within clinical populations [121]. Another study showed that all of the sexual function domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) were significantly lower in women with chronic pelvic pain than in women without chronic pelvic pain [121]. In line with the results of these community based studies, patients with chronic pelvic pain reported more sexual problems such as dyspareunia, problems with desire or arousal and lubrication than women without chronic pelvic pain [121, 122]. One study of patients enrolled in chronic pain treatment programs in England has reported that 73% had pain-related sexual problems [123].

3.2.2.4 Myofascial pain syndromes

The relationship between muscular dysfunction (especially over-activity) and pelvic pain has been found in several studies [124]. Rectal pain treated with pelvic floor muscle therapy is only relieved when patients learn to relax their pelvic floor muscles [125, 126]. The vast majority (92.2%) of men visiting a tertiary centre for pelvic

pain had dysfunction of the pelvic floor muscles. This finding was true regardless of evidence of inflammation (prostatitis or cystitis) [127]. This relationship has been found in chronic prostatitis [128], PBPS [129] and vulvar pain [130]. Dysfunction of the pelvic floor directly affects function of the pelvic viscera and vice versa. Both systems can act as the primary signal to the spinal cord, with a cascade of reactions ascending to the CNS as a result. The muscle itself ends up shortened, leading to restrictions even in a relaxed state.

*3.2.3 **Influence on Quality of Life***

Data on the influence on QoL will be included in a future version of the guidelines.

*3.2.4 **Costs***

No adequate data on costs were found.

*3.2.5 **Risk factors and underlying causes***

The risk factors are unspecific for most of the pain syndromes in the pelvic area. They are described in Section 3.1.5.1. The underlying causes, including the mechanisms for the different clinical pain syndromes are described here.

3.2.5.1 Primary prostate pain syndrome

Pain is the main symptom in PPPS. As a common feature of primary chronic pain syndromes, no single aetiological explanation has been found. One explanation is that the condition probably occurs in susceptible men exposed to one or more initiating factors, which may be single, repetitive or continuous. Several of these potential initiating factors have been proposed, including infectious, genetic, anatomical, neuromuscular, endocrine, immune (including autoimmune), or psychological mechanisms. These factors may then lead to a peripheral self-perpetuating immunological, inflammatory state and/or neurogenic injury, creating acute and then chronic pain. A study showed that chronic but not acute histological inflammation of the prostate was significantly associated with symptomatic progression [131]. Based on the peripheral and the CNS, sensitisation involving neuroplasticity may lead to a centralised neuropathic pain state [132]. This could also explain why tissue damage is not usually found in PPPS. There is growing evidence for a neuropathic origin and association with CNS changes of pain in PPPS, and anxiety appears to be a risk factor for its development [44].

3.2.5.2 Primary bladder pain syndrome

An initial unidentified insult to the bladder, leading to urothelial damage, neurogenic inflammation and pain is thought to be a trigger of PBPS. However, PBPS might be a local manifestation of a systemic disorder. No infection has as yet been implicated. Nevertheless, urinary infections are significantly more frequent during childhood and adolescence, in patients with PBPS in adulthood [133]. Experimental induction of chronic pelvic pain by O-antigen deficient bacterial strains supports the bacterial hypothesis [134]. Pancystitis, with associated perineural inflammatory infiltrates, and mast cell count increase is an essential part of PBPS type 3 C [135], but is rare in non-lesion PBPS [30, 68, 136, 137]. Cystoscopic and biopsy findings in both lesion and non-lesion PBPS are consistent with defects in the urothelial glycosaminoglycan (GAG) layer, which might expose submucosal structures to noxious urine components [138-144] and a consequent cytotoxic effect [145, 146]. Basic and clinical studies indicate that autonomic dysfunction with sympathetic predominance may be implicated in PBPS [147, 148].

An association has been reported between PBPS and non-bladder syndromes such as FM, CFS, IBS, vulvodynia, depression, panic disorders, migraine, sicca syndrome, temporomandibular joint disorder, allergy, asthma and systemic lupus erythematosus [149-153].

Risk of PBPS correlates with a number of non-bladder syndromes in each patient [154]. Recent work showing non-lesion PBPS to have significantly more FM, migraine, temporomandibular joint disorder and depression than PBPS type 3 C patients, which emphasises, the need for subtyping [155].

3.2.5.3 Primary scrotal pain syndrome

Often scrotal pain is not associated with any specific pathology. Pain is perceived in the testes, epididymis, or the vas deferens. The ilioinguinal, genitofemoral and the pudendal nerves innervate the scrotum [156]. Any pathology or intervention at the origin or along the course of these nerves may result in pain perceived in the scrotum [157].

Two special forms of scrotal pain syndrome can be described. The first is post-vasectomy scrotal pain syndrome which occurs following vasectomy. The mechanisms are poorly understood, and for that reason it is considered by some a special form of primary scrotal pain syndrome. Incidence of post-vasectomy pain is 2-20% among all men who have undergone a vasectomy [158]. In men with post-vasectomy pain, 2-6% have

a Visual Analogue Scale (VAS) score > 5 [159]. In a large cohort study of 625 men, the likelihood of scrotal pain after six months was 14.7%. The mean pain severity on a VAS score was 3.4/10. In the pain group, 0.9% had quite severe pain, noticeably affecting their daily life. In this cohort, different techniques were used to perform the vasectomy. The risk of post-vasectomy pain was significantly lower in the no-scalpel vasectomy group (11.7% vs. the scalpel group 18.8%) [160].

The second special form of scrotal pain is post-inguinal hernia repair pain. It is seen as a complication of hernia repair, but in trials it is seldom reported, or it is put under the term chronic pain (not specified). In studies that have explicitly mentioned scrotal pain, there was a difference in incidence between laparoscopic and open hernia repair. In almost all studies, the frequency of scrotal pain was significantly higher in the laparoscopic than in the open group [157, 161]. In one particular study, there was no difference at one year but after five years, the open group had far fewer patients with scrotal pain [162]. Inguinal hernia repair can lead to chronic post-surgical pain (CPSP) in up to 10% of patients at six months [163] and may present with groin and/or scrotal pain. Testicular injury is uncommon (< 1%) but if associated with pain, orchidectomy can lead to symptomatic relief in 2/3 of patients [164]. Careful identification and preservation of nerves has been found to be associated with a reduced risk of chronic pain.

3.2.5.4 Primary urethral pain syndrome

Several mechanisms for the development of primary urethral pain syndrome have been proposed. The intimate relationship of the urethra with the bladder (both covered with urothelium) suggests that primary urethral pain syndrome may be a form of PBPS. Mechanisms thought to be basic for PBPS may also apply to the urethra. This means that the specific testing with potassium has been used to support the theory of epithelial leakage [165, 166]. Another possible mechanism is neuropathic hypersensitivity following urinary tract infection [167]. The relationship with gynaecological and obstetric aspects is unclear. In a small group of patients with urethral pain, it has been found that grand multi-parity and delivery without episiotomy were more often seen in patients with urethral syndrome, using univariate analysis [168].

3.2.5.5 Primary vaginal and vulvar pain syndromes

Pain in the vagina or the female external genital organs is often due to infection or trauma, as a consequence of childbirth or surgery. Pain is usually a precedent to dyspareunia. When the pain persists for more than three months, it can be diagnosed as primary vulvar pain syndrome previously known as “vulvodynia” or “chronic vaginal pain” with no known cause. It is still a poorly understood condition, and therefore difficult to treat.

There are two main sub-types of primary vulvar pain syndrome: generalised, where the pain occurs in different areas of the vulva at different times; and focal, where the pain is at the entrance of the vagina. In primary generalised vulvar pain syndrome, the pain may be constant or occur occasionally, but touch or pressure does not initiate it, although it may make the pain worse. In primary focal vulvar pain syndrome, the pain is described as a burning sensation that comes on only after touch or pressure, such as during intercourse.

The possible causes of primary vulvar pain syndrome are many and include:

- history of sexual abuse;
- history of chronic antibiotic use;
- hypersensitivity to yeast infections, allergies to chemicals or other substances;
- abnormal inflammatory response (genetic and non-genetic) to infection and trauma;
- nerve or muscle injury or irritation;
- hormonal changes.

3.2.5.6 Chronic pelvic pain and prolapse/Incontinence mesh

Continence and prolapse mesh implants were developed as simple flexible polypropylene plastic acting as a scaffold to treat stress urinary incontinence (SUI) and uterovaginal prolapse, respectively. They were deemed easy to insert, but no credence was given as to how safe they were, whether they could be removed should they cause complications, or what to do should they not be effective [169, 170]. Most meshes took less than an hour to implant surgically and most patients were treated as day cases, allowing women to leave hospital quickly and get on with their lives. Therefore, rather than undergo complex traditional surgery, women were offered permanent mesh implants, particularly in the treatment of SUI where they were considered to be the gold standard [171, 172]. However, over the last few years the insertion of mesh has come with significant ‘health and safety warnings’ [173, 174].

For many, mesh was initially seen not just as an effective treatment but as a permanent one. Complications were not thought to be a significant issue and the figure of 1-3% was often quoted. However, we now know the complication rate was closer to 10% [175]. They included chronic pain [176, 177], as well as chronic infections [178], erosion into the surrounding organs including the vagina, urethra and bladder, as well as nerve and musculoskeletal damage affecting mobility [176, 177, 179, 180]. All had a significant impact on the patients' QoL.

It is as a result of severely debilitating complications following mesh implantation [176], that the field of mesh removal medicine and surgery has emerged [181].

Early recognition of possible mesh complications is very important. It is normal to wake up in some degree of discomfort after any surgery. However, if the pain after the operation is very severe and much more than expected after this type of surgery, it can be a sign that there was added trauma to the surrounding organs during the procedure. Most pain is often managed with analgesia, but some women might not fully respond to therapy. If the pain is difficult to treat and does not improve over time, it may become necessary to remove the mesh. Leaving a painful mesh in the pelvis, can lead to chronic pelvic pain. The precise mechanism is unknown but it is thought to be a 'neuro-inflammatory' process [182], as has been proposed in hernia mesh neuralgia. The impact of the mesh, regardless of site, appears to be similar.

3.2.5.7 Chronic post-surgical pain

Chronic post-surgical pain

Chronic pain may develop following surgical procedures and has a significant impact on the individual. The ICD-11 has recently classified chronic post-surgical pain (CPSP) as a chronic pain condition. The definition of CPSP is chronic pain that develops or increases in intensity after a surgical procedure and persists beyond the healing process, i.e., at least three months after the surgery [183].

Chronic post-surgical pain may occur in a significant number of patients, and is more prevalent following some operations rather than others. Procedures with a higher risk of CPSP include limb amputation (30-85%), thoracotomy (5-65%) and mastectomy (11-57%) [184].

Risk factors for CPSP include a number of pre-, peri- and post-operative factors. Younger age, female gender, chronic pain pre-operatively elsewhere, higher number of previous operations, use of opioids and a higher post-operative pain score have been found to be associated with a higher risk of CPSP in a prospective cohort of patients undergoing laparoscopy and laparotomies. Older age, malignant indication for surgery, a higher pre-operative mental health score and the use of epidural analgesia in addition to general anaesthesia were protective [185, 186].

There are a number of procedures specific to the abdomen and pelvis that are associated with an increased risk of chronic pain post-surgery, including bariatric procedures, inguinal hernia repair, vasectomy, hysterectomy and caesarean section. Adhesions are a common cause of chronic abdominal pain but despite this, a SR identified only low level evidence to help guide management of affected individuals [187].

The estimated prevalence of CPSP following bariatric surgery is 30% [188]. In affected individuals careful assessment that may include laparoscopy could identify a treatable cause (such as adhesions, mesenteric defect or cholecystitis) and lead to a significant reduction in post-operative pain [189].

Inguinal hernia repair can lead to CPSP in up to 10% of patients at six months [163] and may present with groin and/or scrotal pain.

The incidence of post vasectomy pain ranges from 2-20% [158, 159]. The risk is significantly lower following the no scalpel technique [160].

The incidence of post-surgical pain following hysterectomy is difficult to determine as pain is a common indication for the operation. When defined as CPSP, rates are estimated at 28-30% [190, 191]. Careful case selection and management of patient expectation is therefore important.

The frequency of caesarean section has increased over time. A meta-analysis has shown a significant incidence of CPSP both at three months and at more than twelve months (15% and 11% respectively) [192], therefore careful counselling is needed in non-emergency cases.

3.2.5.8 Associated conditions in pelvic pain syndromes

Nerve damage

Spinal pathology and any pathology along the course of the nerve involved may result in neuropathic pain in the distribution of these nerves. Neoplastic disease, infection, trauma, surgical incisions and post-operative scarring may result in nerve injury [193].

Pudendal neuralgia is the most often mentioned form of nerve damage in the literature. Anatomical variations may pre-dispose the patient to developing pudendal neuralgia over time or with repeated low-grade trauma (such as sitting for prolonged periods of time or cycling) [194, 195].

The pudendal nerve may be damaged at the level of:

1. The piriformis muscle. For example, as part of a piriformis syndrome: in some cases, the nerve may pass through the muscle and hence be trapped; or in other cases, muscle hypertrophy or spasm is implicated.
2. The sacrospinal/sacrotuberous ligaments, possibly accounting for 42% of cases.
3. Within Alcock's canal (medial to the obturator internus muscle, within the fascia of the muscle), possibly accounting for 26% of cases.
4. Multiple levels in 17% of cases.
5. The site of injury determines the location of perceived pain and the nature of associated symptoms (e.g., the more distal the damage, the less likely the anal region will be involved).

The clinical presentation depends on different factors. There is a wide age range, as one would expect, with a condition that has so many potential causes. It is suggested that, the younger the patient, the better the prognosis. Essentially, the sooner the diagnosis is made, as with any compression nerve injury, the better the prognosis, and older patients may have a more protracted problem [196-198]. Six out of ten cases are observed in women. Some special situations can be listed:

- In orthopaedic hip surgery, pressure from the positioning of the patient, where the perineum is placed hard against the brace, can result in pudendal nerve damage [199, 200]. The surgery itself may also directly damage the nerve. Pelvic surgery such as sacrospinous fixation is clearly associated with pudendal nerve damage in some cases [201, 202]. In many types of surgery, including colorectal, urological and gynaecological, pudendal nerve injury may be implicated.
- Fractures of the sacrum or pelvis may result in pudendal nerve/root damage and pain. Falls and trauma to the gluteal region may also produce pudendal nerve damage if associated with significant tissue injury or prolonged pressure.
- Tumours in the pre-sacral space must be considered. Tumours invading the pudendal nerve may occur and there may also be damage from surgery for pelvic cancer [203].
- The pudendal neuralgia of birth trauma is thought to resolve in most cases over a period of months. However, rarely, it appears to continue as painful neuropathy. Multiple pregnancies and births may predispose to stretch neuropathy in later life. This is more difficult to be certain about [204].
- Child birth and repeated abdominal straining associated with chronic constipation [205] are thought to pre-dispose elderly women to post-menopausal pelvic floor descent and stretching of the pudendal nerve with associated pain. Changes in the hormone status may also be a factor. In Urogenital Pain Management Centres, the commonest associations with pudendal neuralgia appear to be: history of pelvic surgery; prolonged sitting (especially young men working with computer technology); and postmenopausal older women.

Sexual dysfunction

Chronic pelvic pain is a clinical condition that results from complex interactions of physiological and psychological factors and has a direct impact on the social, personal and professional lives of men and women.

Men

Chronic pain as well as its treatment can impair our ability to express sexuality. In an England study, 73% of patients with any chronic pain had some degree of sexual problems as a result of the pain [123]. These problems can occur because of several factors. Psychological factors like decrease in self-esteem, depression and anxiety can contribute to loss of libido. Physiological factors like fatigue, nausea and pain itself can cause sexual dysfunction. Pain medications (opioids, and the selective serotonin re-uptake inhibitors [SSRIs]) can also decrease libido [206] and delay ejaculation. The number of studies on the effects of CPPPS on sexual function is limited. Sexual dysfunction is often ignored because of a lack of standardised measurements. At present, the most commonly used tool is the IIEF questionnaire [145].

The presence of pelvic pain may increase the risk for ED independent of age [207]. On the other hand, cross-sectional data suggest no improvement of lower urinary tract symptoms (LUTS) by an increased frequency of ejaculation [208]. Although mental distress and impaired QoL related to illness could contribute to sexual dysfunction observed in patients with PPPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms suggestive of a more severe inflammatory condition [117]. These arguments are important for the understanding of the close relationship between CPPPS symptoms, disturbed sexuality, impact on QoL, and psychological implications including depression and more failure anticipation thoughts [107-109, 208-210]. Sexual dysfunction heightens anger, frustration and depression, all of which place a strain on the patients' relationships. The female partners of men with sexual dysfunction and depression often present with similar symptoms including pain upon intercourse and depressive symptoms. Men with CPPPS have reported a high frequency of sexual relationship dissolution and psychological symptoms, such as depression and suicidal thinking [107, 211]. Primary Prostate Pain Syndrome patients reported substantial sexual and relationship problems [107, 211]. On the other hand, it was found that men with PPPS did not report significantly decreased sexual satisfaction compared to controls [212]. There is consensus that therapeutic strategies reducing symptoms of pelvic pain are of relevance in relation to changes in sexual function. Also intimacy and having sex can yield positive experiences that will reduce the pain. The CNS plays an important role in this mechanism.

Women

Chronic pelvic pain leads to substantial impairment in QoL and several sexual dysfunctions [119, 213-215]. It seems reasonable to expect that pain, extreme fatigue, depressive mood and pain drugs will affect women's sexuality. Women with CPPPS reported significantly more pain, depression, and anxiety symptoms and were physically more impaired than women in the control group. In comparison with controls, women with CPPPS reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [216]. Patients with CPPPS reported more sexual problems than women with any other type of chronic pain problem [217]. The quality of intimate relationships is closely connected with sexual function [218]. Satisfaction with sexual relationships appears to be associated with higher marital functioning [219]. In addition sexual dissatisfaction is related to sexual dysfunction. When one partner suffers from chronic pain, the ability of both partners to cope with the pain and the extent to which partners are supportive of the chronic pain sufferer have been found to be a predictor of sexual functioning [219].

Approximately two-thirds of patients in another study reported reduced frequency in their sexual relations as a result of CPPPS [220]. One study demonstrated that CPPPS patients reported worse sexual function with regard to desire, arousal, lubrication, orgasm, satisfaction, and more frequent and severe pain with vaginal penetration than women without CPPPS [221]. In an interview with 50 chronic pain sufferers and their spouses, 78% of the pain sufferers and 84% of partners described deterioration, including cessation of their sex life [222]. In a study in patients with back pain, half reported decreased frequency of sex since the onset of chronic pain [123]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. Using the FSFI, women with CPPPS reported worse sexual function in all subscales and total score than women without CPPPS. The largest differences between women with CPPPS and without CPPPS, were seen for the domains of pain and arousal. The total score and the subscales of the FSFI had high levels of internal consistency and test-retest reliability when assessed in a sample of women with CPPPS. The FSFI also showed good ability to discriminate between women with and without CPPPS [221].

Myofascial pain

Myalgia is too often overlooked as a form of chronic pelvic pain. The pelvic floor and adjacent muscles are used in an abnormal way. Studies in the field of chronic prostatitis support the idea that patients with CPPPS have more muscle spasm and increased muscle tone and report pain when the pelvic floor muscles are palpated [223]. Learning pelvic floor muscle relaxation can diminish spasm and pain [224]. Repeated or chronic muscular overload can activate trigger points in the pelvic floor muscles. A report from the Chronic Prostatitis Cohort Study showed that 51% of patients with prostatitis and only 7% of controls had any muscle tenderness. Tenderness in the pelvic floor muscles was only found in the CPPPS group [128].

The first ideas about the neurological aspects of the pelvic floor muscles in relation to chronic pelvic pain were published in 1999. The possibility of CNS changes in the regulation of pelvic floor function was suggested as a mechanism for development of CPPPS. Of the patients presenting with pelvic pain, 88% had poor to absent pelvic floor muscle function [127]. Animal studies on the role of neurogenic inflammation have also elucidated some important phenomena. Irritation of the prostate, bladder and pelvic floor muscles results in expression

of C-fos-positive cells in the CNS. There appears to be convergence of afferent information onto central pathways. Once the central changes have become established, they become independent of the peripheral input that initiated them [225].

Repeated or chronic muscular overload can activate trigger points in the muscle. Trigger points are defined as hyper-irritable spots within a taut band. Other criteria for trigger points are recognition of the pain as 'familiar', and pain on stretching the muscle. Apart from pain, trigger points prevent full lengthening of the muscle, thereby restricting the range of movement. Pain as a result of these trigger points is aggravated by specific movements and alleviated by certain positions. Positions and movements in which the shortened muscle is stretched are painful. Patients know which activities and postures influence pain. Trigger points can be located within the pelvic floor muscles and in adjacent muscles such as the abdominal, gluteal and iliopsoas muscles. Pain is aggravated by pressure on the trigger point (e.g., pain related to sexual intercourse). Pain also worsens after sustained or repeated contractions of pelvic floor muscles (e.g., pain related to voiding or defecation).

3.3 Abdominal aspects of pelvic pain

*3.3.1 **Incidence***

Epidemiological data on IBS and CPPPS are scarce [226]. Chronic Pelvic Pain has been shown to be one of the most common functional disorders in women of reproductive age. The monthly incidence rate of CPPPS published by Zondervan *et al*. was 1.58/1000 [227].

*3.3.2 **Prevalence***

Using a vague definition of continuous or episodic pain situated below the umbilicus over six months, one study reported that CPPPS was one of the most common diagnoses in primary care units in Great Britain [227]. The monthly prevalence rate of CPPPS in this study was 21.5/1,000, with an annual prevalence of 38.3/1,000. The prevalence rates increase significantly with older age and vary significantly between regions in the UK. The overall prevalence of anorectal pain in a sample of USA householders was 6.6% and was more common in women [228]. Irritable bowel syndrome is associated with common gynaecologic problems (endometriosis, dyspareunia, and dysmenorrhoea) [229]. Fifty per cent of women who presented with abdominal pain to the gynaecologic clinic or were scheduled for laparoscopy due to CPPPS had symptoms of IBS [230]. In a survey from Olmsted county, 20% of women reported CPPPS and 40% of those met the criteria for IBS [22]. This overlap of CPPPS and IBS was associated with an increased incidence of somatisation. Not gynaecological surgical procedures but only psychosocial variables predict pain development without a different incidence of IBS in a prospective and controlled study [231]. Clinical features of pelvic floor dysfunction, gynaecological and psychological features, are related to disordered anorectal function in IBS patients, but do not predict physiological anorectal testing.

*3.3.3 **Influence on Quality of Life***

There is little known on health related quality of life (HRQoL) in patients with CPPPS. There is a need to develop validated disease specific HRQoL instruments for CPPPS in addition to sound measurement properties. More data are available in patients with IBS treated at referral centres who have comparable HRQoL scores as patients with other common disorders such as diabetes, end-stage renal disease, and inflammatory bowel disease [232]. Sub-groups of IBS with predominance of diarrhoea or constipation show no difference in HRQoL. Multi-variate analysis shows that HRQoL in patients with IBS is affected by sex and psychological conditions.

*3.3.4 **Costs***

Costs combine direct health-care costs and societal costs (productivity loss) such as under-performance and absenteeism from work. The annual costs to society can be calculated by using the average population earnings. In Germany direct care costs are estimated at €791 and societal costs €995 per patient with IBS per year which may be comparable to patients with CPPPS [233].

*3.3.5 **Risk factors & underlying causes***

Risk factors are covered in Section 3.1.5.

3.4 Summary of evidence and recommendations: CPPPS and mechanisms

Summary of evidence	**LE**
CPPPS mechanisms are well defined and involve mechanisms of neuroplasticity and neuropathic pain.	2
The mechanisms of neuroplasticity and neuropathic pain result in increased perception of afferent stimuli which may produce abnormal sensations as well as pain.	1

End-organ function can also be altered by the mechanisms of neuroplasticity so that symptoms of function can also occur.	1
The diagnosis of a CPPPS as a pain syndrome is essential as it encourages a holistic approach to management with multi-specialty and multi-disciplinary care.	2

Recommendations	Strength rating
All of those involved in the management of chronic pelvic pain should have knowledge of peripheral and central pain mechanisms.	Strong
The early assessment of patients with chronic pelvic pain should involve investigations aimed at excluding disease-associated pelvic pain.	Strong
Assess functional, emotional, behavioural, sexual and other quality of life issues, such as effect on work and socialisation, early in patients with chronic pelvic pain and address these issues as well as the pain.	Strong
Build up relations with colleagues so as to be able to manage CPPPS comprehensively in a multi-specialty and multi-disciplinary environment with consideration of all their symptoms.	Strong

4. DIAGNOSTIC EVALUATION

4.1 General evaluation

4.1.1 ***History***

History is very important for the evaluation of patients with chronic pelvic pain. Pain syndromes are symptomatic diagnoses, which are derived from a history of pain perceived in the region of the pelvis, and absence of other pathology, for a minimum of three months. This implies that specific disease-associated pelvic pain caused by bacterial infection, cancer, drug-induced pathology (e.g., ketamine use) [234], primary anatomical or functional disease of the pelvic organs, and neurogenic disease must be ruled out.

4.1.1.1 Anxiety, depression, and overall function

Distress is best understood in the context of pain and of the meaning of pain to the individual and is best assessed ideographically rather than normatively. Almost all diagnostic measures and standardised instruments of anxiety and depression are designed for people without significant physical problems, so are difficult to interpret in chronic pelvic pain [235].

Anxiety about pain often refers to fears of missed pathology (particularly cancer) as the cause of pain [34], or to uncertainties about treatment and prognosis. These can drive healthcare seeking behaviour. The question: “What do you believe or fear is the cause of your pain?” has been suggested [236]. Anxiety may also concern urinary urgency and frequency that are problematic in social settings.

Depression or depressed moods are common in chronic pain [237], often related to losses consequent to chronic pain (work, leisure activities, social relationships, etc.). Due to the lack of suitable assessment instruments, it is better to ask a simple question such as “How does the pain affect you emotionally?” If the answer gives cause for concern about the patient’s emotional state, further assessment should be undertaken by an appropriately qualified colleague.

Most measures of restricted function are designed primarily for musculoskeletal pain and may emphasise mobility problems rather than the difficulties of the individual with pelvic or urogenital pain. A promising specific measure, UPOINT, was introduced and in a later version the sexological aspects were added [238]. However, it may underassess relevant psychological variables [43]. Generic QoL measures are helpful. If such an instrument is not already used in the clinic, the Brief Pain Inventory [239] provides a broad and economical assessment of interference of pain with various aspects of life, and is available in multiple languages. (For further suggested instruments see [240]).

4.1.1.2 Urological aspects

Pain may be associated with urological symptoms. A detailed history of LUT functions should be taken. Dysfunctions of the LUT may exacerbate symptoms, as pain may interfere with the function of the LUT. Micturition in all its aspects should be addressed. Special attention should be paid to the influence of micturition on the experience of pain.

Primary prostate pain syndrome

Primary prostate pain syndrome is diagnosed from a history of pain perceived in the region of the prostate (convincingly reproduced by prostate palpation), and absence of other LUT pathology, for a minimum of three months. As mentioned above, specific disease-associated pelvic pain must be ruled out. A thorough history is an important first step in the evaluation of PPPS. It should include type of pain and localisation. Pain is often reported in other pelvic areas outside the prostate such as perineum, rectum, penis, testicles and abdomen [49]. In addition, associated LUT symptoms, sexual function, psychological, social and economic factors should be addressed. Determination of the severity of disease, its progression and treatment response can be assessed only by means of a validated symptom-scoring instrument (see Section 4.2.3). These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients in urological practice.

Primary bladder pain syndrome

Primary bladder pain syndrome should be diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by at least one other symptom, such as daytime and/or night-time increased urinary frequency, the exclusion of confusable diseases as the cause of symptoms, and if indicated, cystoscopy with hydrodistension and biopsy (Table 4) [16].

The nature of pain is key to disease definition:

1. pain, pressure or discomfort perceived to be related to the bladder, increasing with increasing bladder content;
2. located suprapubically, sometimes radiating to the groins, vagina, rectum or sacrum;
3. relieved by voiding but soon returns [241, 242];
4. aggravated by food or drink [242].

Primary bladder pain syndrome type 3 can lead to a small capacity fibrotic bladder with or without upper urinary tract outflow obstruction.

4.1.1.3 Gynaecological aspects

A detailed medical history outlining the nature, frequency and site of pain; its relationship to precipitating factors and the menstrual cycle, may help define the aetiology. A menstrual and sexual history, including a history of sexually transmitted diseases, vaginal discharge, as well as previous sexual trauma is mandatory as well as up to date cervical cancer screening. A history of obstetric and/or gynaecological surgery is also warranted, particularly if devices such as synthetic mesh were used.

4.1.1.4 Gastrointestinal aspects

The predominant symptoms that patients are interviewed about are discomfort or pain in relation to their bowel habits, daily activities, and eating. A precise history of dysfunctional voiding or defecation should be asked, ideally applying symptom questionnaires for urinary and anorectal symptoms (e.g., Rome III criteria for anorectal pain). Excessive straining at most defecations, anal digitations in dyssynergic defecation, and a sensation of anal blockage may be found in patients with chronic anal pain. History of anxiety and depression with impaired QoL is often encountered in anorectal functional disorders and should be evaluated.

Diagnostic criteria for primary chronic anal pain syndrome (chronic proctalgia) according to the Rome III criteria are as follows and must include all of the following: chronic or recurrent rectal pain or aching, episodes last at least twenty minutes and exclusion of other causes of rectal pain such as ischaemia, inflammatory bowel disease, cryptitis, intramuscular abscess and fissure, haemorrhoids, prostatitis, and Coccyx Pain Syndrome. These criteria should be fulfilled for the past three months with symptom onset at least six months before diagnosis [243, 244].

The primary chronic anal pain syndrome includes the above diagnostic criteria and exhibits exquisite tenderness during posterior traction on the puborectalis muscle (previously called “Levator Ani Syndrome”). Pathophysiology of pain is thought to be due to over-activity of the pelvic floor muscles.

Primary intermittent chronic anal pain syndrome (proctalgia fugax) consists of all the following diagnostic criteria, which should be fulfilled for three months: recurrent episodes of pain localised to the anus or lower rectum, episodes last from several seconds to minutes and there is no anorectal pain between episodes. Stressful life events or anxiety may precede the onset of the intermittent chronic anal pain syndrome. The attacks may last from a few seconds to as long as 30 minutes. The pain may be cramping, aching or stabbing and may become unbearable. However, most patients do not report it to their physicians and pain attacks occur less than five times a year in 51% of patients.

4.1.1.5 Peripheral nerve aspects

A proportion of patients will be able to relate the onset of pain to an acute event such as surgery, sepsis or trauma, and occasionally, cycling for a prolonged period. Chronic injury is more frequent, such as associated with sitting for prolonged periods over time. Many will be idiopathic.

The pain is classically perceived in the perineum from anus to clitoris/penis. However, less-specific pain distribution may occur, and this may be due to anatomical variation, involvement of branches of the nerve rather that the main nerve, CNS central sensitisation, and consequently, the involvement of other organs and systems in a regional pain syndrome. Other nerves in the vicinity may also be involved, for example, inferior cluneal nerve and perineal branches of the posterior femoral cutaneous nerve. The musculoskeletal system may become involved, confusing the pain picture as aches and pain developing in the muscles due to immobility and disability, possibly magnified by the CNS changes.

Burning is the most predominant adjective used to describe the pain. Crushing and electric may also be used, indicating the two components - a constant pain often associated with acute sharp episodes. Many patients may have the feeling of a swelling or foreign body in the rectum or perineum, often described as a golf or tennis ball. The term pain has different meanings to patients and some would rather use the term discomfort or numbness.

Aggravating factors include any type of pressure being applied, either directly to the nerve or indirectly to other tissue, resulting in pudendal traction. Allodynia is pain on light touch due to involvement of the CNS, and may make sexual contact and the wearing of clothes difficult. These patients often remain standing, and as a consequence, develop a wide range of other aches and pains. Soft seats are often less well-tolerated, whereas sitting on a toilet seat is said to be much better tolerated. If unilateral, sitting on one buttock is common. The pain may be exacerbated by bowel or bladder evacuation.

Pudendal nerve damage may be associated with a range of sensory phenomena. In the distribution of the nerve itself, as well as unprovoked pain; the patient may have paraesthesia (pins and needles); dysaesthesia (unpleasant sensory perceptions usually but not necessarily secondary to provocation, such as the sensation of running cold water); allodynia (pain on light touch); or hyperalgesia (increased pain perception following a painful stimulus, including hot and cold stimuli). Similar sensory abnormalities may be found outside of the area innervated by the damaged nerve, particularly for visceral and striated muscle hyperalgesia.

The cutaneous sensory dysfunction may be associated with superficial dyspareunia, but also irritation and pain associated with clothes brushing the skin. There may also be a lack of sensation and pain may occur in the presence of numbness. Visceral hypersensitivity may result in an urge to defecate or urinate. This is usually associated with voiding frequency, with small amounts of urine being passed. Pain on visceral filling may occur. Anal pain and loss of motor control may result in poor bowel activity, with constipation and/or incontinence. Ejaculation and orgasm may also be painful or reduced.

Many of those suffering from pudendal neuralgia complain of fatigue and generalised muscle cramps, weakness and pain. Being unable to sit is a major disability, and over time, patients struggle to stand and they often become bedbound. The immobility produces generalised muscle wasting, and minimal activity hurts. As a consequence of the widespread pain and disability, patients often have emotional problems, and in particular, depression. Patients with chronic pelvic pain are also often anxious and have the tendency to catastrophise. Depression, catastrophising and disability are all poor prognostic markers. Cutaneous colour may change due to changes in innervation but also because of neurogenic oedema. The patient may describe the area as swollen due to this oedema, but also due to the lack of afferent perception.

4.1.1.6 Myofascial aspects

When taking a history from a patient with pelvic pain, it is important to address the function of all the organs in the pelvic area. The following items certainly should be addressed: lower urinary tract function, anorectal function, sexual function, gynaecological items, presence of pain and psychosocial aspects. One cannot state that there is a pelvic floor dysfunction based only on the history. But there is a suspicion of pelvic floor muscle dysfunction when two or more pelvic organs show dysfunction, for instance a combination of micturition and defecation problems.

4.1.2 ***Physical Evaluation***

The clinical examination often serves to confirm or refute the initial impressions gained from a good history. The examination should be aimed at specific questions where the outcome of the examination may change

management. Prior to an examination, best practice requires the medical practitioner to explain what will happen and what the aims of the examination are to the patient. Consent to the examination should occur during that discussion and should cover an explanation around the aim to maintain modesty as appropriate and, if necessary, why there is a need for rectal and/or vaginal examination. Finally, the risk of exacerbating the pain should form a part of that request. A record of the discussion should be noted. The possibility of the presence of a chaperone should be discussed with the patient. As well as a local examination, a general musculoskeletal and neurological examination should be considered an integral part of the assessment and undertaken. Following the examination, it is good practice to ask the patient if they had any concerns relating to the conduct of the examination and that discussion should be noted.

There is no specific diagnostic test for CPPPS, therefore, procedures are on the one hand directed towards identification and exclusion of specific diseases associated with pelvic pain, and on the other hand may be used for phenotypic description. Abdominal and pelvic examination to exclude gross pelvic pathology, as well as to demonstrate the site of tenderness is essential. It is important to look for abnormalities in muscle function.

Examination of the external genitalia is a part of the evaluation. In patients with scrotal pain, gentle palpation of each component of the scrotum is performed to search for masses and painful spots. The penis and urethra may be palpated in a similar way. Many authors recommend that one should assess cutaneous allodynia along the dermatomes of the abdomen (T11-L1) and the perineum (S3), and the degree of tenderness should be recorded. The bulbocavernosus reflex in the male may also provide useful information concerning the intactness of the pudendal nerves. Clinical pelvic examination should be a single digit examination if possible. The usual bi-manual examination can generate severe pain so the examiner must proceed with caution. A rectal examination is done to look for prostate abnormalities in male patients including pain on palpation and to examine the rectum and the pelvic floor muscles regarding muscle tenderness and trigger points as well as the ability to contract and relax these muscles.

At clinical examination, perianal dermatitis may be found as a sign of faecal incontinence or diarrhoea. Fissures may be easily overlooked and should be searched for thoroughly in patients with anal pain. A rectal digital examination findings may show high or low anal sphincter resting pressure, a tender puborectalis muscle in patients with the Levator Ani Syndrome, and occasionally increased perineal descent. The tenderness during posterior traction on the puborectalis muscle differentiates between Levator Ani Syndrome and unspecified Functional Anorectal Pain and is used in most studies as the main inclusion criterion. Dyssynergic (paradoxical) contraction of the pelvic muscles when instructed to strain during defecation is a frequent finding in patients with pelvic pain. Attention should be paid to anal or rectal prolapse at straining, and ideally during combined rectal and vaginal examination to diagnose pelvic organ prolapse.

A full clinical examination of the musculo-skeletal, nervous and urogenital systems is necessary to aid in diagnosis of pudendal neuralgia, especially to detect signs indicating another pathology. Often, there is little to find in pudendal neuralgia and frequently findings are non-specific. The main pathognomonic features are the signs of nerve injury in the appropriate neurological distribution, for example, allodynia or numbness. Tenderness in response to pressure over the pudendal nerve may aid the clinical diagnosis. This may be elicited by per rectal or per vaginal examination and palpation in the region of the ischial spine and/or Alcock's canal. Muscle tenderness and the presence of trigger points in the muscles may confuse the picture. Trigger points may be present in a range of muscles, both within the pelvis (levator ani and obturator internus muscles) or externally (e.g., the piriformis, adductors, rectus abdominis or paraspinal muscles).

4.2 Supplemental evaluation

If history is suggestive of lower urinary tract, gynaecological, anorectal or other disease of known aetiology, diagnostic work-up should follow respective guidelines.

*4.2.1 **Assessing pelvic pain and related symptoms***

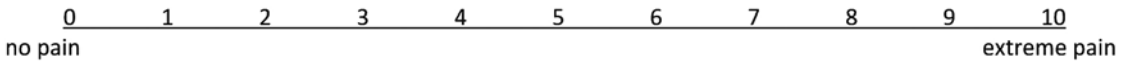
Determination of the severity of pain and associated symptoms, its progression and treatment response can be assessed only by means of a reliable and validated symptom-scoring instrument. These subjective outcome measures are recommended for the basic evaluation and therapeutic monitoring of patients. Pain should always be assessed at presentation and (see below) to identify progression and treatment response. As well as doing this in the clinic, the patient can keep a daily record (pain diary). This may need to include other relevant variables such as voiding, sexual activity, activity levels, or analgesic use.

Increased attention to patient reported outcomes gives prominence to patients' views on their disease and pain diaries, in patients' own environments, improve data quality.

Quality of life should also be measured because it can be very poor compared to other chronic diseases [245, 246]. In a study more pain, pain-contingent rest, and urinary symptoms were associated with greater disability (also measured by self-report), and pain was predicted by depression and by catastrophising (helplessness subscale) [57].

Where the primary outcome of treatment is pain relief, it is useful before starting treatment to agree a clinically useful level of relief [247]. The most reliable methods are:

- a five point verbal scale: none, mild, moderate, severe, very severe pain;
- a VAS score from one to ten;
- an eleven point numerical scale (as below).



Pain assessment ratings are not independent of cognitive and emotional variables [56]. Target outcomes of pain severity, distress and disability co-vary only partly, and improvement in one does not necessarily imply improvement in the others. When the primary outcome is pain its meaning should be anchored in discussion of clinically important difference [247].

Primary prostate pain syndrome

Reliable, valid indices of symptoms and QoL are the NIH-CPSI [248] and the International Prostate Symptom Score (I-PSS) [249].

Primary bladder pain syndrome

Symptom scores may help to assess the patient and act as outcome measures. The O'Leary-Sant Symptom Index, also known as the Interstitial Cystitis Symptom Index (ICSI) was validated in a large study [250].

Gastrointestinal questionnaire

Functional anorectal pain disorders (anorectal pelvic pain) are defined and characterised by duration, frequency, and quality of pain. More complex questionnaires are used in the setting of IBS. The validated IBSSymptom Severity Scale (IBS-SSS) includes the broadest measurement of pain-related aspects [251, 252]. However, as different instruments measure different endpoints of chronic abdominal pain in IBS, a comparison of published studies is often impossible.

Sexual function assessment

In males the most frequent effects on sexual function are ED and premature ejaculation. These can be evaluated by proper questionnaires namely IIEF and PEDT (Premature Ejaculation Diagnostic Tool). In comparison with controls, women with chronic pelvic pain reported significantly more sexual avoidance behaviour, non-sensuality, and complaints of "vaginismus" [205]. The Female Sexual Function Index (FSFI) has been developed as a brief, multi-dimensional self-report instrument for assessing the key dimensions of sexual function in women, which includes desire, subjective arousal, lubrication, orgasm, satisfaction, and pain. The corresponding evidence in men is lacking.

*4.2.2 **Focused myofascial evaluation***

Pelvic floor muscle testing can be done by the medical doctor but a consultation of the pelvic floor by a physiotherapist is a good alternative, but either should have had appropriate training in pelvic assessment. A vaginal or rectal examination is performed to assess the function of the pelvic floor muscles, according to the International Continence Society (ICS) report. This assessment has been tested and shows satisfactory validity and intra-observer reliability. It can therefore be considered suitable for use in clinical practice [253]. Rectal examination is a good way to test the pelvic floor function in men [254]. There is a growing number of reports on the use of ultrasound (US) in establishing the function of the pelvic floor muscles. The exact place in the diagnostic setting needs to be addressed in the future [255]. In a cohort study of 72 men with chronic pelvic pain, the relationship between the locations of the trigger point and the referred pain was examined. Ninety percent of the patients showed tenderness in the puborectalis muscle and 55% in the abdominal wall muscles. Of the patients in whom trigger points were found in the puborectalis, 93% reported pain in the penis and 57% in the suprapubic region. Patients with trigger points in the abdominal muscles reported pain in the penis

(74%), perineum (65%) and rectum (46%) [256]. In addition, a broad musculoskeletal (tender point) evaluation, including muscles outside the pelvis, helps to diagnose the myofascial pain aspects of the pelvic pain in phenotyping pelvic pain patients [257, 258].

*4.2.3 **Neurological***

Injections

An injection of local anaesthetic and steroid at the site of nerve injury may be diagnostic. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [259, 260]. Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical target may be localised by fluoroscopy, computed tomography (CT) guidance, or the use of US. Ultrasound avoids any form of radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed.

Electrophysiological studies

These may reveal signs of perineal denervation, increased pudendal nerve latency, or impaired bulbocavernosus reflex [196, 199, 261-263]. However, for an abnormality to be detected, significant nerve damage is probably necessary. Pain may be associated with limited nerve damage, therefore, these investigations are often normal.

*4.2.4 **Imaging***

Ancillary studies should be performed according to appropriate guidelines for exclusion of diseases with known aetiology presenting with symptoms identical to those of CPPS. Once the latter diagnosis is established, studies can be useful to assess functional abnormalities and phenotype conditions such as PBPS, and primary chronic anal pain syndrome.

Ultrasound

Ultrasound has limited value but may reassure patients. However, over-investigating may be detrimental.

MRI

Magnetic resonance neurography has been increasingly used in specialised centres for the diagnosis of the location (proximal vs. peripheral) and degree (total vs. partial) of nerve injury in the peripheral nervous system, earlier and with higher specificity than conduction studies. This may show benefits for CPPPS in the coming years.

MR defecating proctogram

Magnetic resonance imaging in conjunction with MR defecography has become the most valuable imaging technique to assess anorectal function dynamically. Magnetic resonance imaging studies simultaneously outline the anatomy of the pelvic floor and visualise different structural and functional pathologies, by applying dynamic sequences after filling of the rectum with a viscous contrast medium (e.g., US gel). The following pathologies can be visualised: pelvic floor descent, an abnormal anorectal angle while squeezing and straining, rectal intussusception, rectocele, enterocele and cystocele. However, limitations of MR defecography are the left lateral position and the limited space for the patient, which may reduce the ability to strain and thereby reduce the sensitivity of the method, underestimating the size of entero- and rectoceles as well as the amount of intussusception.

Functional neuroimaging

Functional neuroimaging, functional magnetic resonance imaging (fMRI) is currently being re-evaluated as a research tool and some groups have raised issues around over interpretation [264]. With regards to pain, fMRI findings may represent a pain matrix or may represent non-specific threat processing [265]. Currently this panel cannot recommend fMRI as a clinical tool.

*4.2.5 **Laboratory Tests***

Microbiology tests

Primary prostate pain syndrome

Laboratory diagnosis of prostatitis has been classically based on the four-glass test for bacterial localisation [266]. Besides sterile pre-massage urine (voided bladder urine-2), PPPS shows $< 10^3$ cfu/mL of uropathogenic bacteria in expressed prostatic secretions and insignificant numbers of leukocytes or bacterial growth in

ejaculates. However, this test is too complex for use by practising urologists. Diagnostic efficiency may be enhanced cost-effectively by a simple screening procedure, that is, the two-glass test or pre-post-massage test (PPMT) [267, 268]. Overall, these tests help only a little in the diagnosis of PPPS, because 8% of patients with suggested PPPS have been found to have positive prostatic localisation cultures, similar to the percentage of asymptomatic men [269].

Primary bladder pain syndrome

Urine dipstick and urine culture (including culture for Tuberculosis if sterile pyuria) are recommended in all patients suspected of having PBPS. Urine cytology is also recommended in risk groups.

Gynaecological aspects of chronic pelvic pain

Vaginal and endocervical swabs to exclude infection are recommended. In specific cases, imaging may be required to help rule out a defined pathology such as sacral neuropathy in endometriosis [270].

4.2.6 Invasive tests

Anorectal pain

Anorectal manometry with sensory testing (pressure volume measurement: barostat) may be useful to diagnose dyssynergic defecation and hypersensitivity of the rectum which are typical for patients with CPPPS and IBS. Flexible rectosigmoidoscopy or colonoscopy should be considered in patients with anorectal pain to rule out coincidental colorectal pathology.

Laparoscopy for females

Laparoscopy is perhaps the most useful invasive investigation to exclude gynaecological pathology [271, 272] and to assist in the differential diagnosis of CPPPS in women [273, 274]. Often, it is combined with cystoscopy [275, 276] and/or proctoscopy to help identify the site of multi-compartment pain.

Psychological considerations around laparoscopy

Three very different studies of laparoscopy suggest that it can improve pain through resolving concerns about serious disease [277]. Integrating somatic and psychological assessment from the start rather than dealing with psychological concerns only after excluding organic causes of pelvic pain is helpful [278].

Cystoscopy and bladder biopsy

Despite controversy on the diagnostic and follow-up value of cystoscopy in PBPS [279-283], the panel believes that objective findings are important for diagnosis, prognosis and ruling out other treatable conditions (a standardised scheme of diagnostic criteria will also contribute to uniformity and comparability of different studies) [284]. Endoscopically, PBPS type 3 displays reddened mucosal areas often associated with small vessels radiating towards a central scar, sometimes covered by a small clot or fibrin deposit - the Hunner's lesion [241]. The scar ruptures with increasing bladder distension, producing a characteristic waterfall type of bleeding. There is a strong association between PBPS type 3 and reduced bladder capacity under anaesthesia [285]. Non-lesion disease displays a normal bladder mucosa at initial cystoscopy. The development of glomerulations after hydrodistension is considered to be a positive diagnostic sign although they can be observed without PBPS [286]. Biopsies are helpful in establishing or supporting the clinical diagnosis of both classic and non-lesion types of the disease [139, 165, 284, 287, 288]. Important differential diagnoses to exclude, by histological examination, are carcinoma in situ and tuberculous cystitis.

Table 4: ESSIC classification of PBPS types according to results of cystoscopy with hydrodistension and biopsies [16]

	Cystoscopy with hydrodistension			
	Not done	**Normal**	**Glomerulations[a]**	**Hunner's lesion[b]**
Biopsy				
Not done	XX	1X	2X	3X
Normal	XA	1A	2A	3A
Inconclusive	XB	1B	2B	3B
Positive[c]	XC	1C	2C	3C

[a]*Cystoscopy: glomerulations grade 2-3.*

[b]*Lesion per Fall's definition with/without glomerulations.*

[c]*Histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.*

4.3 Diagnostic algorithm

Figure 1: Diagnosing chronic pelvic pain

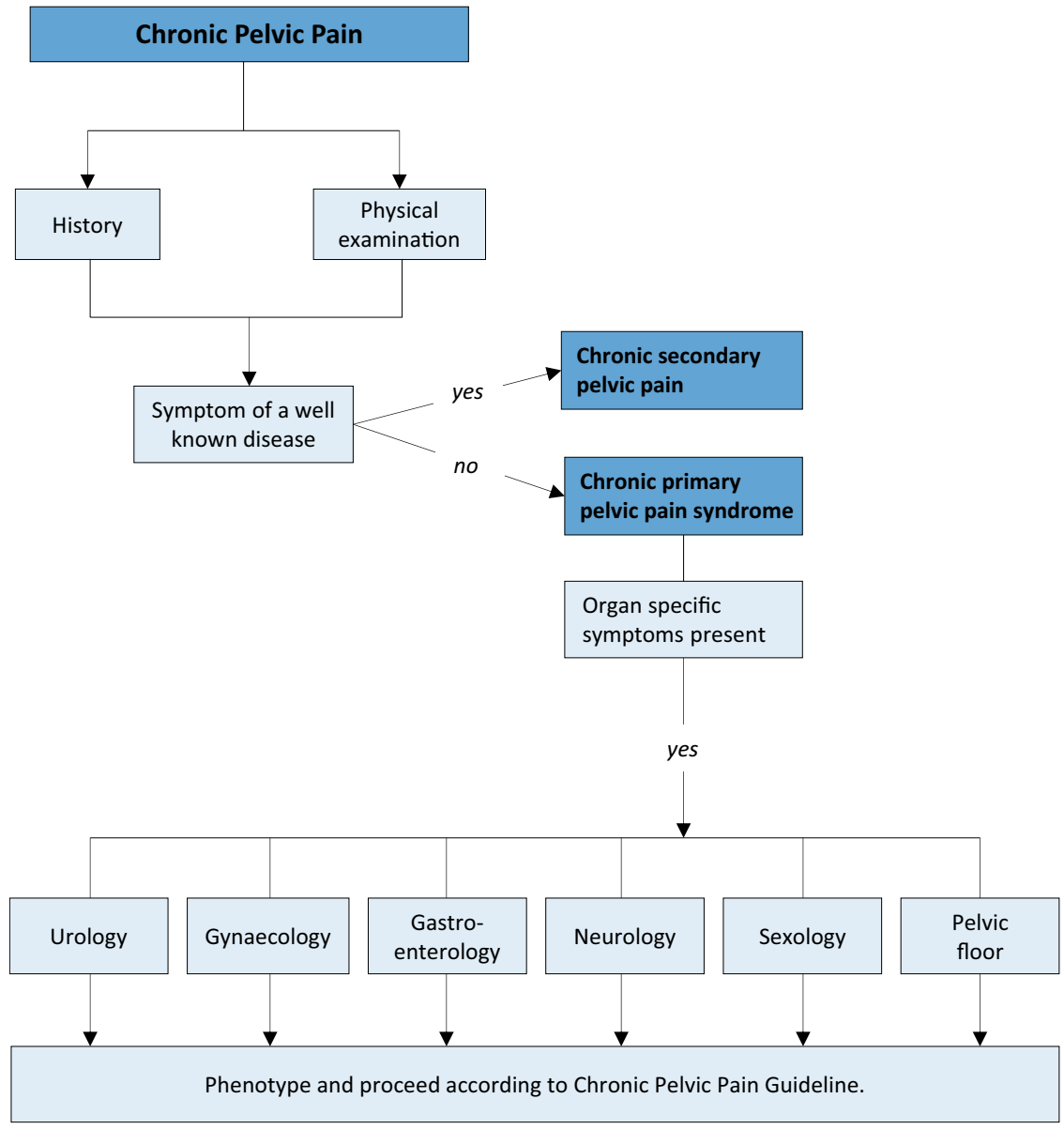


Figure 2: Phenotyping of pelvic pain - UPOINT classification

Phenotyping	Assessment
Urology	Urinary flow, micturition diary, cystoscopy, ultrasound, uroflowmetry.
Psychology	Anxiety about pain, depression and loss of function, history of negative sexual experiences.
Organ specific	Ask for gynaecological, gastro-intestinal, ano-rectal, sexological complaints. Gynaecological examination, rectal examination.
Infection	Semen culture and urine culture, vaginal swab, stool culture.
Neurological	Ask for neurological complaints (sensory loss, dysaesthesia). Neurological testing during physical examination: sensory problems, sacral reflexes and muscular function.
Tender muscle	Palpation of the pelvic floor muscles, the abdominal muscles and the gluteal muscles.
Sexological	Erectile function, ejaculatory function, post-orgasmic pain.

4.4 Other painful conditions without a urological cause

Dysmenorrhoea

Menstrual pain or 'dysmenorrhoea' may be primary or secondary. Primary dysmenorrhoea classically begins at the onset of ovulatory menstrual cycles and tends to decrease following childbirth [273]. Secondary dysmenorrhoea suggests the development of a pathological process, such as endometriosis [272], adenomyosis or pelvic infection, which need to be excluded.

Infection

In pre-menopausal women, a history of Pelvic Inflammatory Disease (PID) must be excluded. A patient's sexual history should be taken along with swabs to exclude chlamydia and gonorrhoea infection. Bacterial and viral genital tract pathogens should also be excluded [289], as they can cause severe pelvic/vaginal/vulvar pain [290] and are associated with ulcerating lesions and inflammation, which may lead to urinary retention [291]. If there is any doubt about the diagnosis, laparoscopy may be helpful, as one of the differential diagnoses is endometriosis.

Endometriosis and adenomyosis

The incidence of endometriosis is rising in the developed world. It has widespread impact on women's lives [292], with pain more important than physical findings in determining QoL [293]. The precise aetiology is unknown, but an association with infertility is recognised [294]. A diagnosis is usually made when a history of secondary dysmenorrhoea and/or dyspareunia exists [295]. On examination, there is often tenderness in the lateral vaginal fornices, reduced uterine mobility, tenderness in the recto-vaginal septum, and on occasion, adnexal masses. Laparoscopy is the most useful diagnostic tool [296-298]. Adenomyosis is associated with augmented pain during menses [299]. It is diagnosed by an US scan of the uterus, which often shows cystic dilatation of the myometrium [300].

Gynaecological malignancy

The spread of gynaecological malignancy of the cervix, uterine body or ovary will cause pelvic pain depending on the site of spread.

Injuries related to childbirth

Trauma occurring at the time of childbirth may lead to chronic pelvic pain related to the site of injury [298]. Female sexual dysfunction is perhaps the commonest presenting problem [301], though increasingly women are reporting other symptoms such as pelvic girdle pain and other genito-pelvic pain of different aetiology [302]. There is often a transient problem with oestrogen deficiency in the post-partum period and during breastfeeding, which can compound this situation. Denervation of the pelvic floor can similarly compound the situation [303].

Pain associated with pelvic organ prolapse and prolapse surgery

Pelvic organ prolapse is often asymptomatic, unless it is so marked that it causes back pain, vaginal pain and skin excoriation [304]. Prolapse is often a disease of older women, and it is often associated with postmenopausal oestrogen deficiency, which may lead to pain associated with intercourse. Prolapse surgery has entailed the use of non-absorbable mesh (usually in the form of "mesh kits"). Although they may have a role in supporting the vagina, they are also associated with several complications including bladder, bowel and vaginal trauma [305], chronic pain [306] and neuropathy [307]. Patients need to be fully evaluated and may need specialised imaging, using contrast mediums if necessary, to make a diagnosis of the possible cause of the pain [308-311].

Haemorrhoids

Chronic pelvic pain is rare in haemorrhoidal disease because endoscopic and surgical treatment is mostly effective in acute disease. The most frequent aetiology of pain without significant bleeding is thrombosed external haemorrhoids or an anal fissure. Haemorrhoidal pain on defecation associated with bleeding is usually due to prolapse or ulceration of internal haemorrhoids. Anaemia from haemorrhoidal bleeding is rare but may arise in patients on anti-coagulation therapy, or those with clotting disorders.

Anal fissure

Anal fissures are tears in the distal anal canal and induce pain during and after defecation. The pain can last for several minutes to hours. Persistence of symptoms beyond six weeks or visible transversal anal sphincter fibres define chronicity. Fissures located off the midline are often associated with specific diseases such as Crohn's disease or anal cancer. Internal anal sphincter spasms and ischaemia are associated with chronic fissures.

Proctitis

Abdominal and pelvic pain in patients with inflammatory bowel disease and proctitis are often difficult to interpret. Faecal calprotectin may help to differentiate between inflammation and functional pain, to spare steroids.

Irritable bowel syndrome

Although IBS can be associated with pelvic pain, the panel consider a full discussion of this topic beyond the scope of these guidelines. A number of high quality clinical guidelines address this topic [243, 312].

4.5 Summary of evidence and recommendations: diagnostic evaluation

4.5.1 Diagnostic evaluation - general

Summary of evidence	LE
Clinical history and examination are mandatory when making a diagnosis.	2a

Recommendation	Strength rating
Take a full history and evaluate to rule out a treatable cause in all patients with chronic pelvic pain.	Strong

4.5.2 Diagnostic evaluation of primary prostate pain syndrome

Summary of evidence	LE
Primary prostate pain syndrome is associated with negative cognitive, behavioural, sexual, or emotional consequences, as well as with symptoms suggestive of LUT and sexual dysfunction.	2b
Primary prostate pain syndrome has no known single aetiology.	3
Pain in PPPS involves mechanisms of neuroplasticity and neuropathic pain.	2a
Primary prostate pain syndrome has a high impact on QoL.	2b
Depression and catastrophic thinking are associated with more pain and poorer adjustment.	3
The prevalence of PPPS-like symptoms is high in population-based studies (> 2%).	2b
Reliable instruments assessing symptom severity as well as phenotypic differences exist.	2b

Recommendations	Strength rating
Adapt diagnostic procedures to the patient. Exclude specific diseases with similar symptoms.	Strong
Use a validated symptom and quality of life scoring instrument, such as the National Institutes of Health Chronic Prostatitis Symptom Index, for initial assessment and follow-up.	Strong
Assess primary prostate pain syndrome-associated negative cognitive, behavioural, sexual, or emotional consequences, as well as symptoms of lower urinary tract and sexual dysfunctions.	Strong

4.5.3 Diagnostic evaluation of primary bladder pain syndrome

Summary of evidence	LE
Primary bladder pain syndrome has no known single aetiology.	3
Pain in PBPS does not correlate with bladder cystoscopic or histologic findings.	2a
Primary bladder pain syndrome Type 3 C can only be confirmed by cystoscopy and histology.	2a
Lesion/non-lesion disease ratios of PBPS are highly variable between studies.	2a
The prevalence of PBPS-like symptoms is high in population-based studies.	2a
Primary bladder pain syndrome occurs at a level higher than chance with other pain syndromes.	2a
Primary bladder pain syndrome has an adverse impact on QoL.	2a
Reliable instruments assessing symptom severity as well as phenotypical differences exist.	2a

Recommendations	Strength rating
Perform general anaesthetic rigid cystoscopy in patients with bladder pain to subtype and rule out confusable disease.	Strong
Diagnose patients with symptoms according to the EAU definition, after primary exclusion of specific diseases, with primary bladder pain syndrome (PBPS) by subtype and phenotype.	Strong
Assess PBPS-associated non-bladder diseases systematically.	Strong
Assess PBPS-associated negative cognitive, behavioural, sexual, or emotional consequences.	Strong
Use a validated symptom and quality of life scoring instrument for initial assessment and follow-up.	Strong

4.5.4 Diagnostic evaluation of scrotal pain syndrome

Summary of evidence	LE
The nerves in the spermatic cord play an important role in scrotal pain.	2b
Ultrasound of the scrotal contents does not aid in diagnosis or treatment of scrotal pain.	2b
Post-vasectomy pain is seen in a substantial number of men undergoing vasectomy.	2b
Scrotal pain is more often noticed after laparoscopic than after open inguinal hernia repair.	1b

4.5.5 Diagnostic evaluation of urethral pain syndrome

Summary of evidence	LE
Primary urethral pain syndrome may be a part of BPS.	2a
Urethral pain involves mechanisms of neuroplasticity and neuropathic pain.	2b

4.5.6 Diagnostic evaluation of gynaecological aspects chronic pelvic pain

Summary of evidence	LE
Laparoscopy is well-tolerated and does not appear to have negative psychological effects.	1b

Recommendations	Strength rating
Take a full uro-gynaecological history in those who have had a continence or prolapse non-absorbable mesh inserted and consider specialised imaging of the mesh.	Strong
Refer to a gynaecologist following complete urological evaluation if there is a clinical suspicion of a gynaecological cause for pain. Laparoscopy should be undertaken in accordance with gynaecological guidelines.	Strong

4.5.7 Diagnostic evaluation of anorectal pain syndrome

Summary of evidence	LE
Tenderness on traction is the main criterion of the chronic anal pain syndrome.	1a

Recommendation	Strength rating
Anorectal function tests are recommended in patients with anorectal pain.	Strong

4.5.8 Diagnostic evaluation of nerves to the pelvis

Summary of evidence	LE
Multiple sensory and functional disorders within the region of the pelvis/urogenital system may occur as a result of injury to one or more of many nerves. The anatomy is complex.	2
There is no single aetiology for the nerve damage and the symptoms and signs may be few or multiple.	1
Investigations are often normal.	2
The peripheral nerve pain syndromes are frequently associated with negative cognitive, behavioural, sexual, or emotional consequences.	1

Recommendations	Strength rating
Rule out confusable diseases, such as neoplastic disease, infection, trauma and spinal pathology.	Strong
If a peripheral nerve pain syndrome is suspected, refer early to an expert in the field, working within a multidisciplinary team environment.	Weak
Imaging and neurophysiology help diagnosis but image and nerve locator guided local anaesthetic injection is preferable.	Weak

4.5.9 Diagnostic evaluation of sexological aspects in chronic pelvic pain

Summary of evidence	LE
Chronic pain can lead to decline in sexual activity and satisfaction and may reduce relationship satisfaction.	2a
Men who reported having sexual, physical or emotional abuse show a higher rate of reporting symptoms of CPPPS.	2b
Sexual dysfunctions are prevalent in men with PPPS.	2b
In men with PPPS the most prevalent sexual complaints are ED and ejaculatory dysfunction.	3
In females with CPPPS all sexual function domains are lower. The most reported dysfunctions are sexual avoidance, dyspareunia and “vaginismus”.	2a
Vulvar pain syndrome is associated with PBPS.	2a
Women with PBPS suffer significantly more from fear of pain, dyspareunia and decreased desire.	2a
Pelvic floor muscle function is involved in the excitement and orgasm phases of sexual response.	3
Chronic pain can cause disturbances in each of the sexual response cycle phases.	2b

Recommendation	Strength rating
Screen patients presenting with symptoms suggestive for chronic primary pelvic pain syndrome for abuse, without suggesting a causal relation with the pain.	Weak

4.5.10 *Diagnostic evaluation of psychological aspects of chronic pelvic pain*

Summary of evidence	LE
There is no evidence that distress generates complaints of pelvic pain, or that multiple symptoms suggest unreality of pain.	2b
Current or recent sexual abuse are possible contributory factors in pelvic pain.	2a

Recommendations	Strength rating
Assess patient psychological distress in relation to their pain.	Strong
Ask patients what they think is the cause of their pain and other symptoms to allow the opportunity to inform and reassure.	Strong

4.5.11 *Diagnostic evaluation of pelvic floor function*

Summary of evidence	LE
The ICS classification is suitable for clinical practice.	2a
Over-activity of the pelvic floor muscles is related to chronic pelvic pain, prostate, bladder and vulvar pain.	2a
Over-activity of the pelvic floor muscles is an input to the CNS causing central sensitisation.	2b
There is no accepted standard for diagnosing myofascial trigger points.	2a
There is a relation between the location of trigger point and the region where the pain is perceived.	3

Recommendations	Strength rating
Use the International Continence Society classification on pelvic floor muscle function and dysfunction.	Strong
In patients with Chronic Primary Pelvic Pain Syndrome it is recommended to actively look for the presence of myofascial trigger points.	Weak

5. MANAGEMENT

The philosophy for the management of chronic pelvic pain is based on a bio-psychosocial model. This is a holistic approach with patients' active involvement. Single interventions rarely work in isolation and need to be considered within a broader personalised management strategy, including self-management. Pharmacological and non-pharmacological interventions should be considered with a clear understanding of the potential outcomes and endpoints. These may well include: psychology, physiotherapy, drugs and more invasive interventions.

Treatment philosophy

Providing information that is personalised and responsive to the patient's problems, conveying belief and concern, is a powerful way to allay anxiety [313]. Additional written information or direction to reliable sources of information is useful; practitioners tend to rely on locally produced material or pharmaceutical products of variable quality while endorsing the need for independent materials for patients [314].

5.1 Conservative management

5.1.1 *Pain education*

It is always valuable to include education about the causes of pain, including eliciting from patients their anxieties about undiscovered pathology and addressing them. Information improves adherence to treatment and underpins self-management, as shown in bladder pain syndrome and in many other painful and non-painful disorders [315].

5.1.2 *Physical therapy*

The physiotherapist is part of the pain management team; (including doctors, psychologists and nurses). The therapeutic options for physiotherapists may not be the same in every country. Physiotherapists can either

specifically treat the pathology of the pelvic floor muscles, or more generally treat myofascial pain if it is part of the pelvic pain syndrome. In most studies that have been done looking at the effect of physiotherapy in pelvic pain, the treatment of the pelvic floor is only part of the pain management. In a review about physiotherapy in women with pelvic pain, it was concluded that recommendations for physiotherapy should be given with caution [316]. The review found six RCTs, of which three showed level 1b evidence with low-risk of bias. One of these three found that Mensendieck somatocognitive therapy showed a pain reduction after one year follow-up of 64%. This approach consists of myofascial relaxation and tension, improving posture and movement in combination with cognitive behaviour therapy (CBT) [317].

Pelvic floor muscle pain

Treating pelvic floor over-activity and myofascial trigger points should be considered in the management of chronic pelvic pain. Treatment should be done by specialised physiotherapists who are trained not only in the musculo-skeletal aspects of pain, but also in the psychological mechanisms and the role of the CNS in chronic pain.

For patients with chronic pelvic pain and dysfunction of the pelvic floor muscles, it is very helpful to learn how to relax the muscles when the pain starts. By doing this, the circle of pain-spasm-pain can be interrupted. In the case of shortened muscles, relaxation alone is not enough. Stretching of the muscle is mandatory to regain length and function. Studies on physical therapy for pelvic floor pain syndrome have been sparse. A single blinded RCT with myofascial physical therapy and general body massage was carried out in patients with prostate or bladder pain. The global response rate (RR) to treatment with massage was significantly better in the prostate than in the bladder pain group (57% vs. 21%). In the prostate pain group, there was no difference between the two treatment arms. In the bladder pain group, myofascial treatment did significantly better than massage. Massage only improved complaints in the prostate pain group. The fact that gender distribution was different in each group is mentioned as a possible confounding factor [318].

Myofascial trigger point release

Treatment of myofascial trigger points can be done by manual therapy, dry needling and wet needling. The evidence for all the different treatments is weak, with most studies showing no significant difference between these techniques, though most studies were small and heterogeneous with regards to the patients and methods. There is no evidence that manual techniques are more effective than no treatment [319]. Most studies of dry needling have compared with wet needling. Different SRs have come to the conclusion that, although there is an effect of needling on pain, it is neither supported nor refuted that this effect is better than placebo [320].

Physiotherapy in PBPS

Transvaginal manual therapy of the pelvic floor musculature (Thiele massage) in PBPS patients with high-tone dysfunction of the pelvic floor significantly improved several assessment scales [321]. The role of specific levator ani trigger point injections in women with chronic pelvic pain has been studied [322]. Each trigger point was identified by intravaginal palpation and injected with bupivacaine, lidocaine and triamcinolone. Seventy-two percent of women improved with the first trigger point injection, with 33% being completely pain-free. Efficacy and safety of pelvic floor myofascial physical therapy has been compared with global therapeutic massage in women with PBPS; global response assessment (GRA) rate was 59% and 26%, respectively. Pain, urgency and frequency ratings, and symptoms decreased in both groups during follow-up, and did not differ significantly between the groups. This suggests that myofascial physical therapy is beneficial in women with PBPS [323].

Primary Anal Pain Syndrome

An RCT demonstrated that biofeedback treatment was superior to electrogalvanic stimulation and massage of the Levator muscle for treating chronic primary anal pain syndrome [125]. One hundred and fifty-seven patients who had at least weekly rectal pain were investigated, but only patients with tenderness on traction of the pelvic floor showed a significant treatment benefit. In patients with tenderness of the puborectalis muscle (Rome II: “Highly likely Levator Ani Syndrome”), 87% reported adequate relief after one month of biofeedback vs. 45% for electrogalvanic stimulation, and 22% for massage. These results were maintained at twelve months with adequate relief after nine sessions of biofeedback in 58% of the whole group (Rome II: “Highly likely” and “Possible Levator Ani Syndrome”), after galvanic stimulation in 27% and massage in 21% of patients. As previously described in dyssynergic defecation, the ability to expel a 50 mL water filled balloon and to relax pelvic floor muscles after biofeedback treatment were predictive of a favourable therapeutic outcome [125]. The pathophysiology of the chronic primary anal pain syndrome is therefore similar to that of dyssynergic defecation, and this favours the role of the pelvic floor muscles in the pathophysiology of both conditions. Other treatment modalities have been less successful.

Treatment of sexual dysfunctions and chronic pelvic pain

Couples often benefit from early referral for relationship and sexual counselling during their treatment course [324]. It needs to be remembered that sexual difficulties will arise as a result of pelvic pain syndromes as well as those disorders potentially being primary. Specific behavioural strategies for women who have urogenital complaints and female sexual dysfunction often include exploring alternatives to sexual intercourse (manual or oral pleasuring), different coital positions (female superior or side lying), and pacing, such as limiting the activity to less than that which causes pain. Planning for the time of intercourse is important, and scheduling a clinic visit after intercourse might be useful to identify specific sites and causes of post-coital flares. The corresponding evidence in men is lacking, but similar principles would apply. Other behavioural changes involve pre- and post-coital voiding, application of ice packs to the genital or suprapubic area [324, 325], and increased use of vaginal dilators, fingers or sex toys. Lubricants can also be used and women with signs of vulvovaginal atrophy may benefit from oestrogen cream [326]. Optimising the pelvic floor muscle is indicated when dysfunction is present and will relieve the pain [327-329].

Other physical therapy interventions

Electromagnetic therapy. A small, sham-controlled, double-blind study of four weeks showed a significant, sustained effect over a one-year period for CPPPS [330].

Microwave thermotherapy. In uncontrolled studies significant symptomatic improvement has been reported from heat therapy, for example, transrectal and transurethral thermotherapy [331, 332].

Extracorporeal shockwave therapy. A small sham-controlled double-blind study of four times weekly perineal extracorporeal shockwave therapy (n=30) in men with CPPPS showed significant improvement in pain, QoL, and voiding compared to the control group (n=30), over twelve weeks [333]. Two other randomised shamcontrolled studies, have been published more recently, one comparing ten treatment sessions over two weeks (n=40 vs. n=40) [334], another with four times weekly treatments (n=20 vs. n=20) [335]. Both concluded there was a significant effect in terms of total NIH-CPSI score and pain at twelve weeks. Unfortunately, no long term effects at 24 weeks could be shown in a published follow-up study of the second [336]. A Cochrane review of non-pharmacological interventions for chronic pelvic pain reported a reduction in symptoms following treatment compared with control and concluded that extracorporeal shockwave therapy may improve symptoms without an increase in adverse events [337]. In addition, a recent SR and meta-analysis concluded that extracorporeal shockwave therapy is effective for the improvement of pain and quality of life, but long-term efficacy was non-significant [338]. Recent publications show a potential role for external shock wave lithotripsy applied to the bladder. In a RCT enrolling 54 patients, improvement in the VAS $\geq$ 3 was 57.1% vs. 19.0% (ESWT vs. placebo; P =.011), at 12 weeks post treatment. However, primary endpoint did not reach significance [339].

Acupuncture. In a small three-arm RCT of CPPPS in men, electro-acupuncture was superior to sham treatment and advice and exercise alone [340]. Another RCT comparing acupuncture (n=50) vs. sham-controlled (n=50), once weekly treatment for six weeks showed significant long lasting improvement at 24 weeks in terms of RR and overall symptom scores [341]. Another RCT showed a significant effect for a follow-up of 32 weeks [342]. Two SRs and meta-analyses were published in 2016 analysing seven RCTs on a total of 471 participants comparing acupuncture to sham control or oral medical treatment [343, 344]. Both came to the conclusion that acupuncture was effective and safe, significantly reducing total NIH-CPSI scores compared to sham or medical treatment, and should be considered as a treatment option. This is in line with the conclusion of a recent Cochrane review [337] on non-pharmacological treatment options. However, the durability of this effect is not known.

Posterior tibial nerve stimulation. See section 5.3.2, Neuromodulation.

Transcutaneous electrical nerve stimulation. See section 5.3.2, Neuromodulation.

*5.1.3 **Psychological therapy***

Psychological interventions may be directed at pain itself or at adjustment to pain in terms of function and mood and reduced health-care use, with or without pain reduction. Ideally, treatment follows general principles and practice in the field of chronic pain [345, 346] but these have been neglected in pelvic pain. Two SRs and meta-analyses of the few heterogeneous trials of psychologically based treatment for pelvic pain [347, 348] found benefits for pain comparable to those from pharmacotherapy over a few months, but this was not sustained at follow-up. Exposure to pain-related fears in women with chronic pelvic pain proved superior to manual therapy in reducing those fears and overall pain disability, albeit assessed only by self-report [349]. The importance of multi-disciplinary treatment is emphasised by several reviews [43, 350, 351] of intervention for diverse chronic pains, but standard multi-component psychologically-based programmes for pelvic pains are mostly in the pilot stages [352], with mixed findings so far [353]. For less disabled and distressed patients treatment can be delivered remotely [354].

*5.1.4 **Dietary treatment***

Scientific data are limited and dietary restriction alone does not produce significant symptomatic relief; however, consider the involvement of a dietician.

5.2 Pharmacological management

*5.2.1 **Drugs for chronic primary pelvic pain syndrome***

In this section the evidence available for specific CPPPSs is presented. Where there is no evidence the reader is directed to the section on analgesics below (Section 5.2.2) where more generic use is discussed. There is a large discrepancy in the treatment effects reported in case series and controlled trials that results from a large placebo effect or publication bias. As a result of the multifactorial origin of for example PPPS, one reason for treatment failure in some large placebo-controlled RCTs, may be the heterogeneity of the patient population [355]. One strategy for improving treatment effects may be stratification of patient phenotypes. A prospective series of phenotypically directed treatment for CPPPS has shown significant improvement of symptoms and QoL [356]. Monotherapeutic strategies for the treatment of CPPPS may fail [357], therefore, most patients require multimodal treatment aimed at the main symptoms, and taking comorbidity into account. In the past ten years, results from RCTs have led to advances in standard and novel treatment options.

5.2.1.1 Mechanisms of action

Mechanisms of action are discussed as appropriate under the drugs headings below.

5.2.1.2 Comparisons of agents used in pelvic pain syndromes

Primary Prostate Pain Syndrome (PPPS)

Anti-inflammatory drugs

For non-steroidal anti-inflammatory agents (NSAIDs), a trial with celecoxib reported that the pain sub-score, QoL sub-score, and total NIH-CPSI score were in favour of the treatment arm vs. placebo, but effects were limited to the duration of therapy [358]. In a meta-analysis, two studies of NSAIDs [269, 358] and one with prednisolone [359] were pooled. Anti-inflammatory drugs were 80% more likely to have a favourable response than placebo. In an updated network meta-analysis with more restrictive inclusion criteria regarding documented outcome measures but a wider spectrum of drugs (including glycosaminoglycans, phytotherapy and tanezumab), a significant effect on total NIH-CPSI scores and treatment response rates could be demonstrated. Overall, a moderate treatment effect has been shown for anti-inflammatory drugs, but larger studies are needed for confirmation, and long-term side-effects have to be taken into account.

α-blockers

Positive results from RCTs of α-blockers, i.e. terazosin [360, 361], alfuzosin [362], doxazosin [363, 364], tamsulosin [365, 366], and silodosin [367] have led to widespread use of α-antagonists in the treatment of PPPS in recent years. Whereas one SR and meta-analysis has not reported a relevant effect of α-blockers due to study heterogeneity [368], another network meta-analysis of α-blockers [367] has shown significant improvement in total symptoms, pain, voiding, and QoL scores. In addition, they had a higher rate of favourable response compared to placebo [relative risk (RR): 1.4; 95% CI: 1.1-1.8, p=0.013]. However, treatment responsiveness, i.e., clinically perceptive or significant improvement, may be lower than expected from the change in mean symptom scores. Overall, α-blockers seem to have moderate but significant beneficial effects. This probably is not the case for long-standing PPPS patients [369]. Future studies should show if longer duration of therapy or some sort of phenotypically directed (e.g., patients with PPPS and relevant voiding dysfunction) treatment strategies will improve treatment outcomes.

Antibiotic therapy

Empirical antibiotic therapy is widely used because some patients have improved with antimicrobial therapy. Patients responding to antibiotics should be maintained on medication for four to six weeks or even longer. Unfortunately, culture, leukocyte and antibody status of prostate-specific specimens do not predict antibiotic response in patients with PPS [370], and prostate biopsy culture findings do not differ from those of healthy controls [371]. The only placebo-controlled RCTs of sufficient quality have been done for oral antibiotic treatment with ciprofloxacin (six weeks) [372], levofloxacin (six weeks) [373], and tetracycline hydrochloride (twelve weeks) [374]. The studies have been analysed in meta-analyses [367, 375]. Although direct meta-analysis has not shown significant differences in outcome measures, network meta-analysis has suggested significant effects in decreasing total symptom, pain, voiding, and QoL scores compared with placebo. Combination therapy of antibiotics with α-blockers has shown even better outcomes in network meta-analysis.

Despite significant improvement in symptom scores, antibiotic therapy did not lead to statistically significant higher response rates [375]. In addition, the sample sizes of the studies were relatively small and treatment effects only modest, mostly below clinical significance. It may be speculated that patients profiting from treatment had some unrecognised uropathogens. If antibiotics are used, other therapeutic options should be offered after one unsuccessful course of a quinolone or tetracycline antibiotic over six weeks. In addition, it is very important that unnecessary antibiotic use is avoided and local resistance patterns are considered. In this regard, the relevant recommendations of the EAU Guidelines on Urological Infections should be followed [376].

5-α-reductase inhibitors

Although a few small pilot studies with 5-α-reductase inhibitors supported the view that finasteride may improve voiding and pain, the first RCT published in a peer-reviewed journal did not support this, although the study lacked power [377]. In another RCT, finasteride provided better amelioration of symptoms compared to saw palmetto over a one-year period, but lacked a placebo-control arm [378]. A six-month placebo-controlled study showed a non-significant tendency towards better outcome in favour of finasteride, possibly because of a lack of statistical power [366]. The NIH-CPSI scores decreased significantly in a subgroup of men enrolled in a prostate cancer risk reduction study treated with dutasteride compared to placebo [367]. Patients (n=427, age 50 to 75, with elevated prostate-specific antigen [PSA]) were included if they had significant "prostatitis-like" symptoms at baseline. Based on the evidence, 5-α-reductase inhibitors cannot be recommended for use in PPPS in general, but symptom scores may be reduced in a restricted group of older men with an elevated PSA [367].

Phytotherapy

Phytotherapy applies scientific research to the practice of herbal medicine. An adequately powered placebo-controlled RCT of a pollen extract (Cernilton) showed clinically significant symptom improvement over a twelve week period in inflammatory PPPS patients (NIH Cat. IIIA) [379]. The effect was mainly based on a significant effect on pain. Another pollen extract (DEPROX 500) has been shown to significantly improve total symptoms, pain and QoL compared to ibuprofen [380]. In an RCT of patients treated with pollen extract suppositories (n=70) vs. oral ibupofen (n=71) over a period of ten days, the authors could find a clinically significant effect up to six months of follow-up including fewer adverse events in the pollen extract group [381]. A SR and meta-analysis of pollen extract for the treatment of PPPS showed significant improvement in overall QoL [382]. Quercetin, a polyphenolic bioflavonoid with documented antioxidant and anti-inflammatory properties, improved NIH-CPSI scores significantly in a small RCT [383]. In contrast, treatment with saw palmetto, most commonly used for "benign prostatic hyperplasia", did not improve symptoms over a one-year period [378]. In a SR and meta-analysis, patients treated with phytotherapy were found to have significantly lower pain scores than those treated with placebo [367]. In addition, overall RR in network meta-analysis was in favour of phytotherapy (RR: 1.6; 95% CI: 1.1-1.6).

Pregabalin is an anti-epileptic drug that has been approved for use in neuropathic pain. In an adequately powered placebo-controlled RCT, which was the only report included in a published Cochrane review [384], a six-week course of pregabalin (n=218) compared to placebo (n=106) did not result in a significant reduction of NIH-CPSI total score [385].

Pentosane polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. One study using oral high-dose (3 x 300 mg/day) demonstrated a significant improvement in clinical global assessment and QoL over placebo in men with PPPS, suggesting a possible common aetiology [386].

Muscle relaxants (diazepam, baclofen) are claimed to be helpful in sphincter dysfunction or pelvic floor/perineal muscle spasm, but there have been few prospective clinical trials to support these claims. In one RCT, a triple combination of a muscle relaxant (thiocolchicoside), an anti-inflammatory drug (ibuprofen) and an α-blocker (doxazosin) was effective in treatment-naïve patients, but not superior to an α-blocker alone [364].

Botulinum toxin type A (BTX-A) for the treatment of CPPPS is an off-label use, but a recent SR identified two RCTs and one non-randomised comparative study assessing intraprostatic BTX-A injections (100-200 units) for treatment of PPPS [387]. All three papers used the NIH-CPSI to score pain. Although two of the studies reported a statistically significant reduction in pain, incomplete data and differences in dose and study methodology precluded calculation of a summary effect estimate for BTX-A-related improvement in pain. No definitive conclusions could be drawn from the review.

Zafirlukast, a leukotriene antagonist, and prednisone in two low-power placebo-controlled studies failed to show a benefit [359, 388]. More recently, a placebo-controlled phase IIa study of tanezumab, a humanised monoclonal antibody that specifically inhibits the pain mediating neurotrophin, nerve growth factor, failed to demonstrate significant effect [389] and should only be used in clinical trials.

Allopurinol
There is insufficient evidence for the use of allopurinol in PPPS [390, 391].

Primary Bladder Pain Syndrome (PBPS)

Treatments of significant value for PBPS

Anti-histamines
Mast cells may play a role in PBPS. Histamine is one of the substances released by mast cells. Histamine receptor antagonists have been used to block the H1 [392] and H2 [393] receptor subtypes, with variable results. A prospective placebo-controlled RCT of hydroxyzine or oral pentosane polysulphate did not show a significant effect [394].

Amitriptyline
Amitriptyline is a tricyclic antidepressant. Several reports have indicated improvement of PBPS symptoms after oral amitriptyline [395]. Amitriptyline has been shown to be beneficial when compared with placebo plus behavioural modification [396]. Drowsiness is a limiting factor with amitriptyline, nortriptyline is sometimes considered instead.

Pentosane polysulphate
Pentosan polysulphate is a semi-synthetic drug manufactured from beech-wood hemicellulose. Subjective improvement of pain, urgency, frequency, but not nocturia, has been reported [397, 398]. Pentosane polysulphate had a more favourable effect in PBPS type 3 C than in non-lesion disease [399]. Response was not dose dependent but related more to treatment duration. At 32 weeks, about half the patients responded. Combination therapy showed a RR of 40% compared to 13% with placebo. For patients with an initial minor response to pentosane polysulphate, additional subcutaneous heparin was helpful [400, 401].

Immunosuppressants
Azathioprine treatment has resulted in disappearance of pain and urinary frequency [402]. Initial evaluation of cyclosporin A (CyA) [403] and methotrexate [404] showed good analgesic effect but limited efficacy for urgency and frequency. Corticosteroids are not recommended in the management of patients with PBPS because of a lack of evidence.

Intravesical Treatments
Intravesical drugs are administered due to poor oral bio-availability establishing high drug concentrations within the bladder, with few systemic side-effects. Disadvantages include the need for intermittent catheterisation which can be painful in PBPS patients, cost and risk of infection [405].

- **Local anaesthetics**

There are sporadic reports of successful treatment of PBPS with intravesical lidocaine [406, 407]. Alkalisation of lidocaine improves its pharmacokinetics [408]. Combination of heparin, lidocaine and sodium bicarbonate gave immediate symptom relief in 94% of patients and sustained relief after two weeks in 80% [409]. Intravesical instillation of alkalised lidocaine or placebo for five consecutive days resulted in significantly sustained symptom relief for up to one month [410].

- **Hyaluronic acid and chondroitin sulphate**

These are described to repair defects in the GAG layer. Despite the fact that intravesical GAG replenishment has been in use for about twenty years for PBPS/IC, most of the studies are uncontrolled and with a small number of patients. Based on the studies available there are differences by virtue of substance classes, whether they are natural GAG layer components, dosage formulations, or concentrations. A recent RCT seems to reinforce the case for GAG layer replenishment, however it lacks a placebo arm [411]. A meta-analysis confirms usefulness of GAG layer replenishment. However most retrieved studies are non-randomised and with scarce numbers [412].

- **Intravesical heparin**

Primary bladder pain syndrome patients were treated with heparin for three months, and over half had control of symptoms, with continued improvement after one year of therapy [413]. Kuo reported another trial of intravesical heparin for three months in women with frequency-urgency syndrome and a positive potassium test. Symptomatic improvement was reported in 80% of PBPS patients [414]. Intravesical heparin plus peripheral neuromodulation in patients with refractory PBPS was studied and it was shown that voiding frequency, pain score and maximum cystometric capacity were significantly better after two and twelve months [415].

- **Hyperbaric oxygen**

This has a moderate effect on a small subgroup of PBPS patients. Disadvantages include high cost, limited availability of treatment sites, and time-consuming treatment [400].

Treatments of limited value for PBPS

Cimetidine

There are limited data to suggest that cimetidine improves symptoms of PBPS in the short-term. Compared with placebo for three months, cimetidine significantly improved symptom scores, pain and nocturia, although the bladder mucosa showed no histological changes in either group [416].

Prostaglandins

Misoprostol is a prostaglandin that regulates various immunological cascades. After three months of treatment with misoprostol, fourteen out of 25 patients had significantly improved, with twelve showing a sustained response after a further six months [417]. The incidence of adverse drug effects was 64%.

L-Arginine

Oral treatment with the nitric oxide (NO) synthase substrate L-arginine decreases PBPS-related symptoms [418, 419]. Nitric oxide is elevated in patients with PBPS [420]. However, others have not demonstrated symptomatic relief or changes in NO production after treatment [421, 422].

Oxybutynin is an anti-cholinergic drug used in overactive detrusor dysfunction. Intravesical oxybutynin combined with bladder training improves functional bladder capacity, volume at first sensation, and cystometric bladder capacity [423]. However, an effect on pain has not been reported.

Duloxetine (a serotonin-noradrenaline re-uptake inhibitor antidepressant with a licence for the management of neuropathic pain) did not significantly improve symptoms of PBPS [424]. Administration was safe, but tolerability was poor due to nausea. Based on these preliminary data, duloxetine cannot be recommended for treatment of PBPS.

Primary Scrotal Pain Syndrome (PSPS)

Treatment of primary scrotal pain syndrome is based on the principles of treating chronic pain syndromes, as described throughout these guidelines.

In men with pain post inguinal hernia repair, there is limited evidence from case series showing that neurectomy of the damaged nerves can lead to symptomatic benefit [192, 425].

For scrotal pain post vasectomy, affected men may find that reversal of vasectomy can cure symptoms especially in those in whom patency is achieved [426]. In a prospective RCT, pulsed radio-frequency to the ilioinguinal and genitofemoral nerves is associated with high rates of symptomatic improvement (80%) but follow up was limited to three months [427]. The evidence for epididymectomy is poor but if considered, is less likely to provide benefit if the epididymis has a normal sonographic appearance [428].

Chronic gynaecological pain

It is difficult to compare the wide variation of drugs from an efficacy and safety perspective as they have such diverse uses/indications. In those gynaecological patients where chronic pelvic pain is unrelated to any of the well-defined conditions, it is often difficult to determine a therapeutic pathway other than a multi-disciplinary chronic abdomino-pelvic pain management plan. A Cochrane review suggests there may be some evidence (moderate) supporting the use of progestogens [347]. Though efficacious, physicians need to be knowledgeable of progestogenic side effects (e.g., weight gain, bloatedness - the most common adverse effects) which can stop some patients from accepting such medication. Gonadotropin-releasing hormone

(GnRH), such as goserelin, are also thought to help such pain. However, when compared with progestogens, their efficacy remains limited. The quality of evidence is generally low and drawn from single studies [347]. Gonadotropin-releasing hormone on the other hand binds to specific receptors on pituitary gonadotrophs, leading to desensitisation and consequently to suppressed gonadotropin secretion. By contrast, GnRH antagonists compete with GnRH for receptors thus gonadotrophin secretion, which may be beneficial in certain clinical applications, such as reducing the size of fibroids, endometrial bleeding and endometriosis [429].

Pelvic Floor, Abdominal and Chronic Anal Pain

Botulinum toxin type A (pelvic floor)

Pelvic floor muscle over-activity plays a role in CPPPS. Botulinum toxin type A, as a muscle relaxant, can be used to reduce the resting pressure of the pelvic floor muscles and injection of the puborectalis and pubococcygeus muscles has been used to treat spasm of the levator ani A pilot study of 12 women with pelvic floor muscle overactivity as defined by a vaginal resting pressure > 40 cm H_2O on vaginal manometry reported a reduction in resting pressure with improvement in dyspareunia and dysmenorrhoea, but no significant changes in non-menstrual pelvic pain scores [430]. A recent SR including three RCTs comparing BTX-A with saline injections into the pelvic floor found no benefit in pain scores at six months follow-up despite a reduction in pelvic floor pressure [387].

Botulinum toxin type A has been injected into trigger points. It is more expensive than lidocaine and has not been proven to be more effective [431]. Reviews do not support the injection of BTX-A into trigger points [432].

Botulinum toxin type A can also be injected at the sphincter level to improve urination or defecation. Relaxation of the urethral sphincter alleviates bladder problems and secondarily the spasm. In a cohort study of thirteen patients with CPPPS, BTX-A was injected into the external urethral sphincter. Subjectively, eleven patients reported a substantial change in pain symptoms, from a score of 7.2 to 1.6 on a VAS [433].

Intermittent chronic primary anal pain syndrome

Due to the short duration of the episodes, medical treatment and prevention is often not feasible. Inhaled β-2 adrenergic agonist salbutamol was effective in an RCT in patients with frequent symptoms and shortened pain duration [434]. Other treatment options are topic diltiazem and BTX-A [435]. However, there is still some controversy regarding the duration of pain of intermittent chronic and chronic primary anal pain syndrome. Randomised controlled trials often use different definitions, extending the pain duration (with a shift to chronic pain) in order to include more patients and to better evaluate the study-drug action.

Abdominal pain associated with Irritable Bowel Syndrome

Linaclotide, a minimally absorbed peptide guanylate cyclase-C agonist at a dose of 290 µg once daily significantly improved abdominal pain (48.9% vs. 34.5% placebo-treated) and bowel symptoms associated with IBS with constipation over 26 weeks of treatment [436]. Diarrhoea was the most common adverse event in patients treated with linaclotide (4.5%). Although it is known to overlap with IBS pelvic pain, effect on the latter was not assessed in this study.

Delta-9-tetrahydrocannabinol (THC) shows only equivocal evidence of analgesic effects in chronic primary abdominal pain. In a recently published phase II trial, no difference was found between THC tablet and a placebo tablet in reducing pain outcome in patients with chronic abdominal pain [437].

*5.2.2 **Analgesics***

If the use of simple analgesics fails to provide adequate benefit, then consider using neuropathic agents, and if there is no improvement, consider involving a specialist pain management centre with an interest in pelvic pain. Chronic pelvic pain is well defined and involves multiple mechanisms as described in previous sections.

The management requires a holistic approach with biological, psychological and social components. Few studies have specifically looked at medications used in CPPPS [438], therefore, a wider look at the literature has been undertaken and further specific research is required. The agents concerned are divided for ease of description. Combinations often provide a greater benefit than individual agents [439]. They may also allow lower individual dosages and thus minimise side-effects. The aim of using these drugs is to allow patients to improve their QoL. This is best measured by assessing their function as well as pain severity. If the use of these agents does not allow this, then they should be withdrawn. Unfortunately, the failure of one agent does not exclude potential benefit of an alternative. If the benefit is limited by side-effects, then the lowest effective dose should be found (by dose titration). Sometimes, patients will prefer a higher level of pain and have fewer side-effects.

5.2.2.1 Mechanisms of action

Mechanisms of action are discussed as appropriate under the drug headings below.

5.2.2.2 Comparisons within and between groups in terms of efficacy and safety

Paracetamol (acetaminophen)

Paracetamol is a well-tolerated analgesic in a class of its own. This is an antipyretic analgesic with a central mechanism of action [440]. It is often available over the counter without prescription. A review questions its routine use as a first-line analgesic based on inadequate evidence of efficacy in many pain conditions including dysmenorrhoea [441]. It will not be effective for all patients and individual responses should be reviewed when deciding on longer term use.

Non-steroidal anti-inflammatory agents

These agents are anti-inflammatory, antipyretic analgesics that act by inhibiting the enzyme cyclooxygenase (COX). They have a peripheral effect, hence their use in conditions involving peripheral or inflammatory mechanisms. They are commonly used for pelvic pain; many are available over the counter and are usually well-tolerated. There is insufficient evidence to suggest one NSAID over another for pelvic pain. Guidelines for use of NSAIDs and COX-2 selective agents have been developed. They have more side-effects than paracetamol, including indigestion, headaches and drowsiness.

The evidence for their benefit in chronic pelvic pain is weak or non-existent and is often limited by side-effects. For pelvic pain in which inflammatory processes are considered important, such as dysmenorrhoea [442], NSAIDs are more effective than placebo and paracetamol, but with a higher incidence of side-effects. For pelvic pain in which central mechanisms may be incriminated, such as endometriosis [443] then the evidence is lacking for NSAIDs despite their common use.

At a practical level, if NSAIDs are considered for use, they should be tried (having regard for the cautions and contraindications) and the patient reviewed for improvement in function as well as analgesia. If this is not achieved, or side-effects are limiting, then they should be withdrawn.

Neuromodulators

These agents are not simple analgesics but used to modulate neuropathic or centrally mediated pain. There are several classes commonly used with recognised benefits in pain medicine. They are taken on a regular basis and all have side-effects that may limit their use and have the potential to be dependance-forming. In the UK, NICE has reviewed the pharmacological management of neuropathic pain [444]. The evidence for treatment of CPPPS is lacking but is present for other painful conditions. For this chapter, most of the evidence is from non-pelvic pain sources. The general method for using these agents is by titrating the dose against benefit and side-effects. The aim is for patients to have an improvement in their QoL, which is often best assessed by alterations in their function. It is common to use these agents in combination but studies comparing different agents against each other, or in combination, are lacking. Some of these agents are also used for specific conditions. Early identification of neuropathic pain with a simple questionnaire could facilitate targeted therapy with neuromodulators [58].

Antidepressants

Tricyclic antidepressants

The tricyclic antidepressants (TCAs) have multiple mechanisms of action and are frequently limited by their side-effects. Tricyclic antidepressants have a long history of use in pain medicine and have been subjected to a Cochrane review [445], suggesting that they are effective for neuropathic pain. Amitriptyline is the most commonly used at doses from 10-75 mg/day (sometimes rising to 150 mg/day). This is titrated against benefit or side-effects and should be taken at night [444]. Nortriptyline and imipramine are used as alternatives.

Other Antidepressants

Duloxetine is a SNRI antidepressant licensed for use in depression, SUI and neuropathic pain. There is evidence of benefit in diabetic neuropathy and fibromyalgia at a dose of 60 mg/day [446, 447]. Side-effects are common and may result in its discontinuation.

Anticonvulsants

Anticonvulsants are commonly used in the management of neuropathic pain. There are general studies and some looking more particularly at pelvic pain. Individual agents have been systematically reviewed. Their use is suggested in the NICE Neuropathic Pain Guidelines [444].

Carbamazepine has a long history of use in neuropathic pain. Evidence exists for its benefit [448]. Trials trend to be of short duration, showing only moderate benefit. There are side-effects; some of which may be serious. It is no longer a first choice agent. Other anticonvulsant agents are available with fewer serious side-effects.

Gabapentinoids
There is a growing awareness and evidence of the risk for dependence and misuse of gabapentinoids [449]. A formal assessment of efficacy against benefit and side-effects (both pain and QoL) is required with the patient in order to determine the lowest effective dose and if longer-term treatment is to be used.

Gabapentin is commonly used for neuropathic pain and has been systematically reviewed [450, 451]. This demonstrates good evidence for posterpatic neuralgia and diabeltic neuropathy but evidence for other neuropathies is limited. A double-blind RCT looking at PCPPS in women with no obvious pathology demonstrated no benefits but higher levels of side effect [451].

Pregabalin is a commonly used neuromodulator with good evidence of efficacy in some neuropathic conditions [452]. The dose for benefit is in the range of 300-600 mg/day. Evidence for central neuropathic pains is inadequate. Some patients do gain moderate to significant benefit but most will gain no benefit and then the drug should be discontinued. Other agents can be used in the management of neuropathic pain but they are best administered by specialists in the management of pain whom are familiar with their use. They tend to be considered after the standard options have been exhausted. As with all good pain management, they are used as part of a comprehensive multi-dimensional management plan.

Opioids
Over recent years opioids have been used extensively for managing chronic non-cancer pain. There is increasing evidence that their role is limited in this population but may be beneficial for a small number of patients at a low dose in a managed setting [453]. There is clear evidence of harm and significant professional, public and political interest. Their use is beneficial for both acute pain and for cancer pain management particularly towards the end of life.

Often patients will stop taking oral opioids due to side effects or insufficient analgesic effect [454]. There is clear evidence of harm including effects on the endocrine and immune systems as well as a growing understanding of opioid-induced hyperalgesia [455]. There is limited guidance on the best method for tapering the dose of opioids with the aim of stopping or finding the lowest effective dose [456].

Opioids should only be used in conjunction with a management plan with consultation between clinicians experienced in their use. It is suggested that a pain management unit should be involved along with the patient and their primary care physician. Ensure there are arrangements for formal monitoring, follow-up and review. If opioids are used and the pain remains, then they are not working and should be stopped even if there is no alternative [455].

The risk of harm increases substantially at doses above 120 mg/day morphine equivalence [455] and guidance suggests regular (at least annual) review for patients with over 50 mg/day morphine equivalence and pain specialist involvement above 90 mg/day morphine equivalence [457].

There are well-established guidelines for the use of opioids in pain management as well as considering the potential risks [455, 457]. Opioid reduction and optimisation should be undertaken where opioids are not providing clear measurable benefit. There is also information available online for patients [455]. Opioids Aware is a web-based resource for patients and healthcare professionals, jointly produced by the Faculty of Pain Medicine of Royal College of Anaesthetists and Public Health England, to support prescribing of opioid medicines for pain. https://fpm.ac.uk/opioids-aware.

Cannabinoids
There has been increasing interest and changes in national regulations regarding the use of cannabinoids for medicinal use. Regarding pain the evidence base for the use of cannabinoids is weak [458-460] and further well conducted clinical trials are necessary. This is an area where further guidance and research is likely in the coming years.

5.3 Further management

5.3.1 ***Nerve blocks***

Nerve blocks for pain management are usually carried out by specialists in pain medicine as part of a broader management plan [461]. They may have a diagnostic or therapeutic role. Textbooks have been written on the subject and practitioners using them should be trained in appropriate patient selection, indications, risks and benefits. Many such interventions also require understanding and expertise in using imaging techniques to perform the blocks accurately. Diagnostic blocks can be difficult to interpret due to the complex mechanisms underlying the painful condition or syndrome. Sustained but limited benefit may lead to more permanent procedures (e.g., radiofrequency procedures). There is a weak evidence base for these interventions for chronic non-malignant pain [462].

Pudendal Neuralgia

The role of injections may be divided into two. First, an injection of local anaesthetic with or without steroids at the sight of nerve injury may produce a therapeutic action [463, 464]. The second possible benefit is diagnostic. It has already been indicated that when the pudendal nerve is injured there are several sites where this may occur. Differential block of the pudendal nerve helps to provide information in relation to the site where the nerve may be trapped [260, 465-472].

Infiltration at the ischial spine requires the use of a nerve stimulator/locator. Both motor (anal contraction) and sensory endpoints may be noted. The anatomical endpoint may be localised by fluoroscopy, CT guidance, or the use of US, the latter avoids any radiation, whereas CT guidance involves a significant amount of radiation. Currently, fluoroscopy is probably the imaging technique most frequently used because it is readily available to most anaesthetists that perform the block. Currently, infiltration of the pudendal nerve within Alcock's canal is primarily undertaken with the use of CT. As well as injecting around the pudendal nerve, specific blocks of other nerves arising from the pelvis may be performed. Pulsed radio frequency stimulation has been suggested as a treatment [473]. Pulsed radio frequency lesioning for pudendal neuralgia is being developed with a paper demonstrating potential benefit. Follow-up is short term and further research is required to better elucidate its place in management [474].

5.3.2 ***Neuromodulation***

The role of neuromodulation in the management of pelvic pain should only be considered by specialists in pelvic pain management. These techniques are used as part of a broader management plan and require regular follow-up. The research base is developing and the techniques broadening (e.g., spinal cord stimulation, sacral root stimulation, dorsal root ganglion stimulation or peripheral nerve stimulation). These are expensive interventional techniques for patients refractory to other therapies. Neuromodulation is still finding its role in pelvic pain management. There has been growing evidence but more detailed, high quality research is required [475]. Its role in overactive bladder (OAB) and faecal incontinence is more robust but is limited for pain. Two SRs have evaluated neuromodulation techniques for CPPS [476, 477]. Both studies concluded that neuromodulation may be effective in reducing pain and improving QoL in patients with CPPS; however, studies were of a low quality and long-term results were needed.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive technique used in many pain conditions. A SR identified twelve studies of TENS in chronic pelvic pain conditions including four RCTs [476]. All RCTs demonstrated a significant reduction in pain following twelve weeks of treatment for pain conditions including dysmenorrhoea and CPPPS. Pain was also found to improve following TENS for provoked vestibular pain. There was conflicting data with regard to improvement of QoL following TENS; where validated questionnaires were used, no significant improvement was found, whereas in trialist-defined studies, an improvement was seen in TENS for dysmenorrhea and CPPPS. The beneficial effects of a course of TENS may be sustained; one study demonstrating a persistent benefit at 43 months in 73% of men with CPPPS and another demonstrating a prolonged significant improvement in women with provoked vestibular pain at ten months post-treatment. Where reported there were no adverse events recorded. Transcutaneous electrical nerve stimulation could offer an effective non-invasive treatment option for patients with CPPPS.

Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive technique that can be use in an outpatient setting. Two SRs have shown that PTNS is effective in reducing pain in patients with CPPPS [476, 477]. Three RCTs identified showed a significant improvement in pain scores and QoL as measured by validated questionnaires. Where recorded, adverse events were rare and minor including temporary slight pain at application site and haematoma.

Sacral Nerve Stimulation

Sacral nerve stimulation (SNS) is an invasive technique requiring sedation or general anaesthesia for implantation of a device following trial stimulation. A SR review identified ten studies of SNS in CPPPS, either retrospective case series or prospective cohort studies and no RCTs. Where reported, a mean of 69% of participants progressed to implantation of device following test stimulation (range 52-91%). All studies reported an improvement in pain, statistically significant in five studies. Quality of Life was measured in three studies and a significant improvement demonstrated in two of three studies. There was a large variation in adverse events reported ranging from 0-50%. Complications not requiring surgical intervention included pain, failure of device, wound infection and seroma. Re-operation rate ranged between 11-50% for complications including lead migration, systemic infection, intrathecal implantation, loss of efficacy and erosion. In clinical practice, a patient should be appropriately counselled regarding the need for a period of trial stimulation and whilst there may be an improvement in symptoms, this should be weighed against a notable complication rate.

A SR review in 2018 identified fourteen studies. In all, 403 patients had undergone percutaneous nerve evaluation and/or SNM stage 1 and 54.8%) had progressed to the permanent implantation stage, which is similar to that reported previously. The cause of pain was reported to be IC/BPS in 170 cases (42.2%). Visual Analogue Scale pain scores were available pre- and post-SNM in 210 patients and overall improvement in pain scores was significant. Sacral nerve stimulation is a promising treatment option for refractory chronic pelvic pain. This is mainly supported by level 2b studies. Randomised prospective studies are warranted to compare SNS vs. other modalities for chronic pelvic pain treatment. Further studies are needed to compare antegrade vs. retrograde approaches [478].

Other neuromodulation techniques

A variety of other techniques of neuromodulation for patients with CPPPS were identified by SRs [476, 479]. These techniques include intravaginal electrical stimulation for women with CPPPS, pudendal nerve stimulation for CPPPS, spinal cord stimulation for pudendal neuralgia, transcutaneous interferential electrical stimulation for IBS, electrical acupuncture for dysmenorrhoea and electrical stimulation/biofeedback and electromagnetic stimulation for men with CPPPS. Whilst an improvement in pain has been reported in these studies, it is noted that they are largely of low quality and further work is needed in this area to enable robust clinical recommendations to be made. Neuromodulaution in combination with hormonal treatment in deep endometriosis may have some benefit [480].

*5.3.3 **Surgery***

Primary Bladder Pain Syndrome (PBPS)

Bladder distension

Although bladder hydrodistension is a common treatment for PBPS, the scientific justification is scarce. It can be part of the diagnostic evaluation, but has limited therapeutic role.

Hydrodistension and Botulinum toxin type A

Botulinum toxin type A may have an anti-nociceptive effect on bladder afferent pathways, producing symptomatic and urodynamic improvements [481]. Treatment with hydrodistension and hydrodistension plus intravesical BTX-A has been compared [482]. There was symptomatic improvement in all patients. However, in the hydrodistension-only group, 70% returned to their previous symptoms after one month, while in the BTX-A-treated patients, VAS score and functional and cystometric bladder capacity improved at three months. Botulinum toxin type A trigonal-only injection seems effective and long-lasting as 87% of patients reported improvement after three months follow-up [483]. Over 50% reported continued benefit nine months after the first treatment. When re-treatment was needed, similar results were obtained. Adverse effects of BTX-A administration for IC/PBPS were significantly less than for OAB syndrome, namely in increased post-void residual volumes and decreased voiding efficiency [484]. Recent RCTs have reported benefits and long efficacy of BTX-A administration [485-488], but a summary estimate for overall change in pain following BTX-A injections was not possible in a recent SR [387]. Conflicting data on results hinders issuance of a clear guideline for the use of Botox in PBPS phenetypes. Despite this, the American Urological Association (AUA) guidelines panel has upgraded BTX-A treatment from fifth to a fourth line treatment [489].

Results of treatment with intravesical plasma rich (PRP) injections are also being explored. A recent prospective trial, showed that patients with GRA (global response assessment) ≥ 2, had success rates at one month and at three months after the 4th PRP injection, of 70.6% and 76.7%, respectively. The VAS pain score, frequency, and nocturia showed a significant decrease (all $p < 0.05$). However further studies are needed to validate findings [490].

Transurethral resection, coagulation and laser ablation

Endourological destruction of bladder tissue aims to eliminate urothelial Hunner lesions. Since the 1970s, resection and fulguration have been reported to achieve symptom relief, often for more than three years [491-493]. Prolonged amelioration of pain and urgency has been described for transurethral laser ablation as well [494].

Open Surgery for PBPS

Primary bladder pain syndrome is benign and does not shorten life, thus operative procedures rank last in the therapeutic algorithm. There is no evidence that it relieves pain. Surgery for PBPS is only appropriate as a last resort for patients with refractory disease. Major surgery should be preceded by thorough pre-operative evaluation, with an emphasis on determining the relevant disease location and subtype. If surgery is considered, the panel's advice is to refer the patient to a specialist centre experienced in managing CPPPS with a multi-disciplinary team approach.

Four major techniques are common:

1. Urinary diversion without cystectomy is performed to minimise the duration and complexity of surgery, but complications related to the retained bladder commonly occur. Reports that un-resected PBPS bladders cease to induce symptoms after loss of contact with urine are scarce [103, 495].
2. Supratrigonal cystectomy with bladder augmentation represents the most favoured continence-preserving surgical technique particularly in younger patients [496]. Various intestinal segments have been used [497-499]. After orthotopic bladder augmentation, bladder emptying may be incomplete so intermittent self-catheterisation may be required. A study on female sexuality after cystectomy and orthotopic ileal neobladder showed pain relief in all patients and improvement in sexual function items in women who remained sexually active [500]. Pregnancies with subsequent lower-segment Caesarean section have been reported after ileocystoplasty [501].
3. Subtrigonal or simple cystectomy refers to removal of the entire bladder at the level of the bladder neck. This approach has the benefit of removing the trigone as a possible disease site, but at the cost of requiring ureteric re-implantation. Trigonal disease is reported in 50% of patients and surgical failure has been blamed on the trigone being left in place [502], especially in patients with non-lesion type disease [503, 504]. However, in a previous study all patients were rendered symptom-free by supratrigonal resection compared to 82% of those undergoing subtrigonal cystectomy. Voiding dysfunction is most likely to occur following trigonal resection and patients considering augmentation and especially substitution procedures must be capable of accepting, performing and tolerating self-catheterisation [505].
4. Cystectomy with formation of an ileal conduit is considered for patients with PBPS who develop recurrent pain in the augmented bladder, continent pouch after enterocystoplasty or continent urinary diversion. Re-tubularisation of a previously used bowel segment to form a urinary conduit has been recommended [506].

Primary Prostate Pain Syndrome

There is no evidence for surgical management, including transurethral incision of the bladder neck, radical transurethral resection of the prostate or, in particular, radical prostatectomy in the management of chronic pain in patients with PPPS. A large Chinese RCT of circumcision combined with a triple oral therapy (ciprofloxacin, ibuprofen, tamsulosin) vs. oral therapy alone has been published for patients with PPPS (total n=774) [507]. It is hypothesised that there may be some immunological interaction via pathogenic antigen presenting cells in the foreskin with CD4+ T cells causing auto-immunity to the prostate gland. They reported an improvement in total NIH-CPSI score and subdomain scores at twelve weeks. However, despite a large cohort, the study results are questionable because of the weak theoretical background, and a potential large placebo effect lacking a sham control. In addition, no long-term effectiveness has been reported. Before having an impact on recommendations, the results of this study have to be independently confirmed and the treatment effect must persist.

Primary Testicular Pain Syndrome

Microsurgical denervation of the spermatic cord can be offered to patients with testicular pain. In a long-term follow-up study, patients who had a positive result on blocking the spermatic cord were found to have a good result following denervation [508, 509].

Chronic Primary Anal and Abdominal Pain Syndrome

Chronic primary anal pain syndrome after stapled procedures, such as hemorrhoidopexy or stapled transanal rectal resection may respond to excision of the scarred staple line as shown in 21 consecutive patients with

an overall improvement of pain in 85.7% of patients undergoing scar excision surgery [510]. An early scar excision before three to six months after pain onset was associated with better pain relief. Adhesiolysis is still in discussion in the pain management after laparotomy/laparoscopy for different surgical indications in the pelvis and entire abdomen. An RCT has shown, that adhesiolysis is associated with an increased risk of operative complications, and additional operations and increased health care costs as compared to laparoscopy alone [511].

Primary Urethral Pain Syndrome

There is no specific treatment that can be advised. Management should be multi-disciplinary and multi-modal [512]. Laser therapy of the trigonal region may be a specific treatment. One trial comparing two forms of laser reported good results, but did not compare with sham treatment [513]. The majority of publications on treatment of primary urethral pain syndrome have come from psychologists [167, 514].

Presumed intra-abdominal adhesions

In gynaecological patients with CPPPS and presumed adhesions, there is no consensus as to whether adhesiolysis should be performed to improve pain [514].

Extensive surgery for endometriosis is challenging and is still considered to be controversial, as there is at least one RCT showing no benefit in pain relief after the removal of early extensive endometriosis vs. sham surgery [272, 515]. Increasingly treatment algorithms are being developed using a multi-disciplinary approach, although none have thus far been proven clinically [516]. In patients with adenomyosis, the only curative surgery is hysterectomy but patients can benefit from hormonal therapy and analgesics (see Section 5.2.2).

Pudendal neuralgia and surgery

Decompression of an entrapped or injured nerve is a routine approach and probably should apply to the pudendal nerve as it applies to all other nerves. There are several approaches and the approach of choice probably depends upon the nature of the pathology. The most traditional approach is transgluteal; however, a transperineal approach may be an alternative, particularly if the nerve damage is thought to be related to previous pelvic surgery [198, 260, 517-520]. Currently, there has been only one prospective RCT (transgluteal approach) [519]. This study suggests that, if the patient has had the pain for less than six years, 66% of patients will see some improvement with surgery (vs. 40% if the pain has been present for more than six years). Surgery is not the answer for all patients. On talking to patients that have undergone surgery, providing the diagnosis was clear-cut, most patients were grateful to have undergone surgery but many still have symptoms that need management.

Chronic Pelvic Pain and Prolapse/Incontinence Mesh

Removing an existing mesh is a complex procedure [521]. Each patient is approached on an individual basis depending on the type of mesh and extent of complications [522]. The complexity of surgery often involves removal of dense scar tissue, reformation of inflamed vaginal skin and surgical reconstruction of the urethra and bladder [523]. Such surgery requires specialist skills, best provided within a multi-disciplinary tertiary setting. Possible complications as a result of this surgical removal include bleeding, infection, damage to surrounding organs as well as LUTS, persistent chronic pain and recurrent SUI, which occurs after mesh removal [524].

Removal of mesh, whilst complex, does have beneficial outcomes generally, which are also durable particularly for chronic pain [525]. However, the long-term consequences after the mesh is removed still can include, not only chronic persistent pain but also autoimmune responses and complex neuropathies affecting the pelvis and lower limbs [526, 527]. Some of these can be treated effectively using a multi-disciplinary pain medicine approach [528]. In other cases, the residual symptoms may require the input of an immunologist, rheumatologist or other symptom-defined specialist.

The alternative to continence and prolapse mesh surgery is dependent on the clinical findings at the time. They include behavioural change, physiotherapy (for SUI and Grade I-II uterovaginal prolapse) or traditional surgical techniques. Studies have shown that over 70% who committed to physiotherapy for SUI often did not need any further intervention [529]. Many clinicians are reverting to conservative measures first, before re-considering surgery. Clinicians are also now retraining in traditional continence surgical techniques, which existed in the pre-mesh era, such as the Burch colposuspension and autologous fascial sling; as well as traditional utero-vaginal prolapse techniques such as vaginal hysterectomy, sacrospinous fixation and fascial repair of vaginal wall prolapse.

5.4 Summary of evidence and recommendations: management

5.4.1 Management of primary prostate pain syndrome

Summary of evidence	LE
Phenotypically directed treatment may improve treatment success.	3
α-blockers have moderate treatment effect regarding total pain, voiding, and QoL scores in PPPS.	1a
Antimicrobial therapy has a moderate effect on total pain, voiding, and QoL scores in PPPS.	1a
Non-steriodal anti-inflammatory drugs have moderate overall treatment effects on PPPS.	1a
Phytotherapy has some beneficial effect on pain and overall favourable treatment response in PPPS.	1a
Pentosane polysulphate improves global assessment and QoL score in PPPS.	1b
There are insufficient data on the effectiveness of muscle relaxants in PPPS.	2b
Pregabalin is not effective for the treatment of PPPS.	1b
Botulinum toxin type A injection into the pelvic floor (or prostate) may have a modest effect in PPPS.	2b
Acupuncture is superior to sham acupuncture in improving symptoms and QoL.	1a
Posterior tibial nerve stimulation is probably effective for the treatment of PPPS.	1b
Extracorporeal shock wave therapy is probably effective over the short term.	1b
There are insufficient data supporting the use of other surgical treatments, such as transurethral incision of the bladder neck, transurethral resection of the prostate, or radical prostatectomy in patients with PPPS.	3
Cognitive behavioural therapy designed for PPPS may improve pain and QoL.	3

Recommendations	Strength rating
Offer multimodal and phenotypically directed treatment options for Primary Prostate Pain Syndrome (PPPS).	Weak
Use antimicrobial therapy (quinolones or tetracyclines) over a minimum of six weeks in treatment-naïve patients with a duration of PPPS less than one year.	Strong
Use α-blockers for patients with a duration of PPPS less than one year.	Strong
Offer high-dose oral pentosane polysulphate in PPPS.	Weak
Offer acupuncture in PPPS.	Strong
Offer non-steroidal anti-inflammatory drugs (NSAIDs) in PPPS, but long-term side-effects have to be considered.	Weak

5.4.2 Management of primary bladder pain syndrome

Summary of evidence	LE
There is insufficient data for the long-term use of corticosteroids.	3
Limited data exist on effectiveness of cimetidine in PBPS.	2b
Amitriptyline is effective for pain and related symptoms of PBPS.	1b
Oral pentosane polysulphate is effective for pain and related symptoms of PBPS.	1a
Oral pentosane polysulphate plus subcutaneous heparin is effective for pain and related symptoms of PBPS, especially in initially low responders to pentosane polysulphate alone.	1b
Intravesical lidocaine plus sodium bicarbonate is effective in the short term.	1b
Intravesical pentosane polysulphate is effective, based on limited data, and may enhance oral treatment.	1b
There are limited data on the effectiveness of intravesical heparin.	3
Intravesical chondroitin sulphate may be effective.	2b
There is insufficient data for the use of bladder distension as a therapeutic intervention.	3
Hydrodistension plus BTX-A is superior to hydrodistension alone.	1b
Intravesical BCG is not effective in PBPS.	1b
Transurethral resection (coagulation and laser) may be effective in PBPS type 3 C.	3
Sacral neuromodulation may be effective in PBPS.	3
Pudendal nerve stimulation is superior to sacral neuromodulation for treatment of PBPS.	1b
Avoidance of certain foods and drink may reduce symptoms.	3
Outcome of cystectomy for PBPS is variable.	3

Recommendations	Strength rating
Offer subtype and phenotype-oriented therapy for the treatment of Primary Bladder Pain Syndrome (PBPS).	Strong
Always consider offering multimodal behavioural, physical and psychological techniques alongside oral or invasive treatments of PBPS.	Strong
Offer dietary advice.	Weak
Administer amitriptyline for treatment of PBPS.	Strong
Offer oral pentosane polysulphate for the treatment of PBPS.	Strong
Offer oral pentosane polysulphate plus subcutaneous heparin in low responders to pentosane polysulphate alone.	Weak
Do not recommend oral corticosteroids for long-term treatment.	Strong
Offer intravesical hyaluronic acid or chondroitin sulphate before more invasive measures.	Weak
Offer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.	Weak
Offer intravesical heparin before more invasive measures alone or in combination treatment.	Weak
Do not use bladder distension alone as a treatment of PBPS.	Weak
Consider submucosal bladder wall and trigonal injection of botulinum toxin type A plus hydrodistension if intravesical instillation therapies have failed.	Strong
Offer neuromodulation before more invasive interventions.	Weak
Only undertake ablative and/or reconstructive surgery as the last resort and only by experienced and PBPS-knowledgeable surgeons, following a multi-disciplinary assessment including pain management.	Strong
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in PBPS type 3 C only.	Strong

5.4.3 Management of scrotal pain syndrome

Summary of evidence	LE
Microsurgical denervation of the spermatic cord is an effective therapy for primary scrotal pain syndrome.	2b
Vasovasostomy is effective in post-vasectomy pain.	2b

Recommendations	Strength rating
Inform about the risk of post-vasectomy pain when counselling patients planned for vasectomy.	Strong
Do open instead of laparoscopic inguinal hernia repair, to reduce the risk of scrotal pain.	Strong
In patients with testicular pain improving after spermatic block, offer microsurgical denervation of the spermatic cord.	Weak

5.4.4 Management of primary urethral pain syndrome

Summary of evidence	LE
There is no specific treatment for primary urethral pain syndrome.	4

5.4.5 Management of gynaecological aspects of chronic pelvic pain

Summary of evidence	LE
Therapeutic options, including pharmacotherapy and surgery, can treat endometriosis effectively.	1b
Psychological treatment (CBT or supportive psychotherapy) can improve pain and sexual and emotional function in vaginal and vulvar pain syndrome.	1b
Most gynaecological pain conditions (including dysmenorrhea, post-mesh insertion and gynaecological malignancy) can be treated effectively using pharmacotherapy.	3
All other gynaecological conditions (including obstetric injury, pelvic organ prolapse) can be treated effectively using surgery.	2

Recommendations	Strength rating
Involve a gynaecologist to provide therapeutic options such as hormonal therapy or surgery in well-defined disease states.	Strong
Provide a multi-disciplinary approach to pain management in persistent disease states.	Strong
All patients who have developed complications after mesh insertion should be referred to a multi-disciplinary service (incorporating pain medicine and surgery).	Strong

5.4.6 Management of primary anorectal pain syndrome

Summary of evidence	LE
Biofeedback is the preferred treatment for Chronic Primary Anal Pain Syndrome.	1a
Electro-galvanic stimulation is less effective than biofeedback.	1b
Available evidence fails to confirm effectiveness of BTX-A in management of Chronic Primary Anal Pain Syndrome.	3
Percutaneous tibial nerve stimulation is effective in anal pain.	3
Sacral neuromodulation is effective in anal pain.	3
Inhaled salbutamol is effective in intermittent Chronic Primary Anal Pain Syndrome.	3

Recommendations	Strength rating
Undertake biofeedback treatment in patients with chronic anal pain.	Strong
Offer percutaneous tibial nerve stimulation in Chronic Primary Anal Pain Syndrome.	Weak
Offer sacral neuromodulation in Chronic Primary Anal Pain Syndrome.	Weak
Offer inhaled salbutamol in intermittent Chronic Primary Anal Pain Syndrome.	Weak

5.4.7 Management of pudendal neuralgia

Summary of evidence	LE
There are multiple treatment options with varying levels of evidence.	3

Recommendation	Strength rating
Neuropathic pain guidelines are well-established. Use standard approaches to management of neuropathic pain.	Strong

5.4.8 Management of sexological aspects in chronic pelvic pain

Summary of evidence	LE
Pelvic floor muscle physical therapy may offer relief of pain and reduction in sexual complaints.	2b

Recommendations	Strength rating
Offer behavioural strategies to the patient and his/her partner to reduce sexual dysfunctions.	Weak
Offer pelvic floor muscle therapy as part of the treatment plan to improve quality of life and sexual function.	Weak

5.4.9 Management of psychological aspects in chronic pelvic pain

Recommendation	Strength rating
For chronic pelvic pain with significant psychological distress, refer patient for chronic pelvic pain-focused psychological treatment.	Strong

5.4.10 *Management of pelvic floor dysfunction*

Summary of evidence	LE
Myofascial treatment is effective.	1b
Biofeedback improves the outcome of myofascial therapy.	1a

Recommendations	Strength rating
Apply myofascial treatment as first-line treatment.	Weak
Offer biofeedback as therapy adjuvant to muscle exercises, in patients with anal pain due to an overactive pelvic floor.	Strong

5.4.11 *Management of chronic/non-acute urogenital pain by opioids*

Recommendations	Strength rating
Opioids and other drugs of addiction/dependency should only be prescribed following multi-disciplinary assessment and only after other reasonable treatments have been tried and failed.	Strong
The decision to instigate long-term opioid therapy should be made by an appropriately trained specialist in consultation with the patient and their family doctor.	Strong
Where there is a history or suspicion of drug abuse, involve a psychiatrist or psychologist with an interest in pain management and drug addiction.	Strong

6. EVALUATION OF TREATMENT RESULTS

6.1 Evaluation of treatment

For patients with chronic primary visceral pain, a visit to the clinician is important because they can ask questions, talk about how the process is going and have some time with the caregiver who understands the nature of their pain. First evaluation should take place after about six weeks to see if the treatment has been successful or not. When necessary adaptations are made and a next evaluation is planned.

6.1.1 *Treatment has not been effective*

6.1.1.1 *Alternative treatment*

In cases where the treatment initiated did not have enough effect, an alternative approach is advised. The first thing to do is a thorough evaluation of the patients' or care providers' adherence to the treatment that was initiated. Ask the patient if they have taken the medication according to the prescription, if there were any side effects and if there were any changes in pain and function. Adjustment of medication or dose schemes might help. Another important thing to do is to read the reports of other caregivers, for example, the physiotherapist and the psychologist. Has the therapy been followed until the end, what was the opinion of the therapist about the changes that were observed? In cases where the sessions had been terminated by the patient, ask the patient why they made that decision. Check if the patient has understood the idea behind the therapy that had been prematurely stopped.

6.1.1.2 *Referral to next envelope of care*

If patients and doctors conclude that none of the therapies given showed enough effect, then referral to a next envelope of care is advised. Unfortunately, the terminology used to describe the nature and specialisation level of centres providing specialised care for visceral pain patients is not standardised and is country-based. This does not facilitate easy referral schemes. It is advised that patients are referred to a centre that is working with a multi-disciplinary team and nationally recognised as specialised in pelvic pain. Such a centre will re-evaluate what has been done and when available, provide specialised care.

6.1.1.3 *Self-management and shared care*

Patients who find themselves confronted with CPPPS, for which there is no specific treatment option available, will have to live with their pain. They will need to manage their pain, meaning that they will have to find a way to deal with the impact of their pain on daily activities in all domains of life. Self-help programmes may be advised

and can be of help. The patient may also benefit from shared care, which means that a caregiver is available for supporting the self-management strategies. Together with this caregiver, the patient can optimise and use the management strategies.

*6.1.2 **Treatment has been effective***

In cases where treatment has been effective, the caregiver may pay attention to fall-back prevention. If the patient feels the same pain again, it helps to start at an early stage with the self-management strategies that he/she has learned during the former treatment. By doing so they will have the best chance of preventing the re-development of pelvic pain syndromes.

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8. CONFLICT OF INTEREST

All members of the EAU Chronic Pelvic Pain Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publically accessible through the European Association of Urology website https://uroweb.org/guidelines/.

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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Muscle-invasive and Metastatic Bladder Cancer

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Guidelines Panel for Muscle-invasive and Metastatic Bladder Cancer (MIBC) have prepared these guidelines to help urologists assess the evidence-based management of MIBC and to incorporate guideline recommendations into their clinical practice.

Separate EAU guidelines documents are available addressing upper urinary tract (UUT) tumours [1], non-muscle-invasive bladder cancer (TaT1 and carcinoma *in situ*) (NMIBC) [2], and primary urethral carcinomas [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel consists of an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiologist and radiotherapists. In the course of 2021 two patient representatives formally joined the MIBC Guidelines Panel.

Section 5.3 -MIBC and health status, was developed with the assistance of Prof.Dr. S. O'Hanlon, consultant geriatrician, International Society of Geriatric Oncology (SIOG) representative and member of the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Prostate Cancer Guidelines Panel. The MIBC Panel is most grateful for his support.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=panel

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version.

Several scientific publications are available (the most recent paper dating back to 2021 [4], as are a number of translations of all versions of the EAU MIBC Guidelines. All documents are accessible through the EAU website: http://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU published its first guidelines on bladder cancer (BC) in 2000. This document covered both NMIBC and MIBC. Since these conditions require different treatment strategies, it was decided to give each condition its own guidelines, resulting in the first publication of the MIBC Guidelines in 2004. This 2022 document presents a limited update of the 2021 version.

*1.4.2 **Summary of changes***

New relevant references have been identified through a structured assessment of the literature and incorporated in the various chapters of the 2022 EAU MIBC Guidelines resulting in new sections and added and revised recommendations in:

- Section 5.2 Imaging for staging of MIBC, and in particular Section 5.2.1 Local staging of MIBC, with the provision of a revised recommendation.

*5.2.6 **Summary of evidence and guidelines for staging in muscle-invasive bladder cancer***

Summary of evidence	LE
In local staging, MRI is superior to CT in terms of differentiating T1 from T2 disease.	2b

Recommendation	Strength rating
Use CT urography unless it is contraindicated for reasons related to contrast administration or radiation dose, in that case use MRI.	Strong

Considerable new data was added to:

- Section 7.1 Neoadjuvant therapy
- Section 7.1.2 Role of cisplatin-based chemotherapy; this section was revised with considerable new data added.
- Section 7.3.5 Laparoscopic/robotic-assisted laparoscopic cystectomy; a new section on stricture formation has been included.
- Section 7.3.6.2 Different types of urinary diversion, in particular Section 7.3.6.2.1 Uretero-cutaneostomy
- Section 7.6.2 Role of adjuvant immunotherapy has been completely revised including a new recommendation.

7.6.3 ***Summary of evidence and guidelines for adjuvant therapy***

Summary of evidence	**LE**
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting for patients with high-risk MIBC who have and have not received neoadjuvant chemotherapy have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Results for adjuvant treatment with immune-checkpoint inhibitors in high-risk MIBC are conflicting: nivolumab improved DFS (Checkmate 274) whereas atezolizumab did not (IMvigor 010).	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

Recommendation	**Strength rating**
Discuss immunotherapy with nivolumab with selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

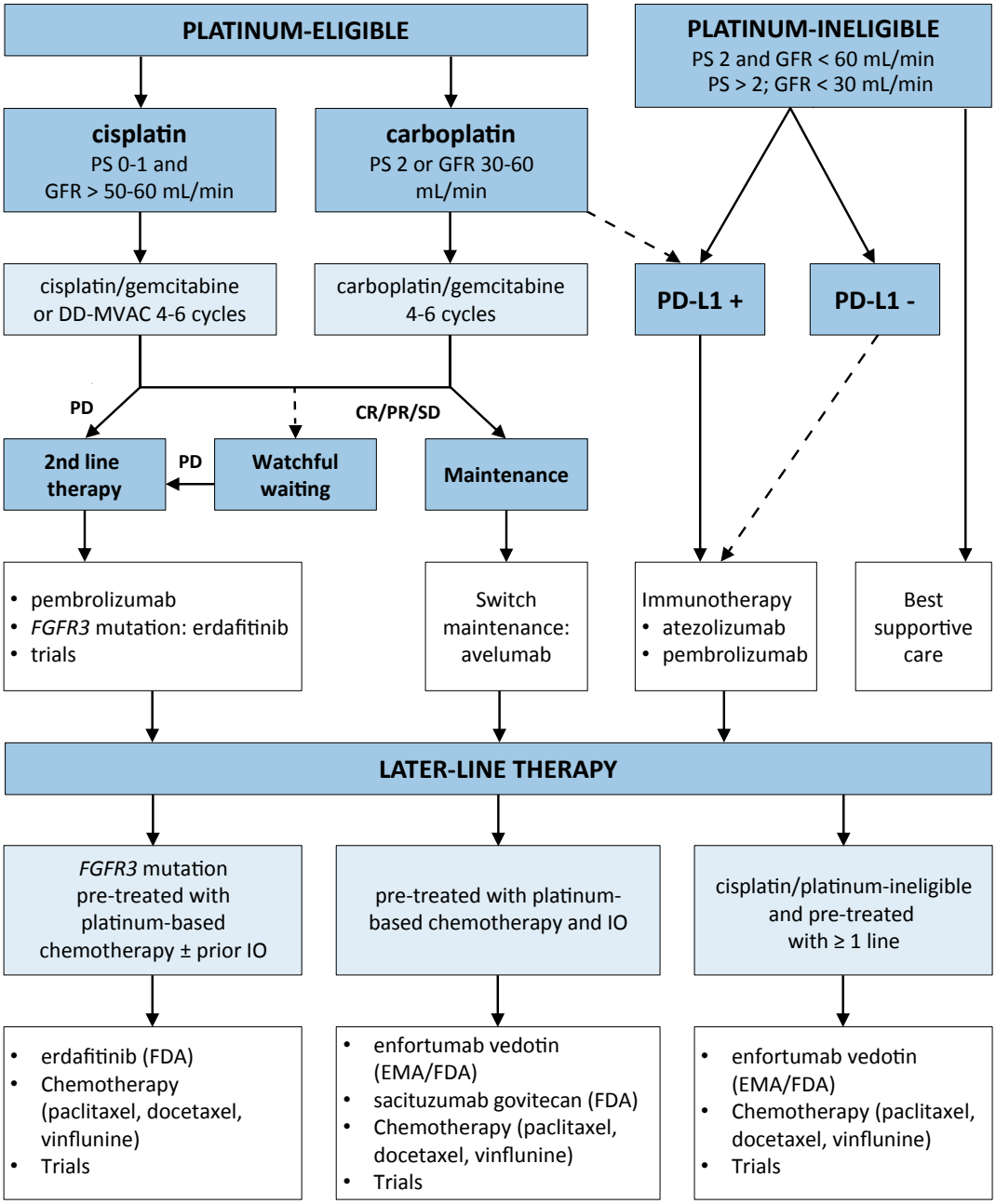
- Section 7.7 Metastatic disease was completely revised, resulting in the inclusion of new recommendation.

7.7.9 ***Summary of evidence and guidelines for metastatic disease***

Summary of evidence	**LE**
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-L1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b
PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-1 status).	1b

Recommendation	**Strength rating**
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy).	Weak

Figure 7.2: Flow chart for the management of metastatic urothelial cancer*



**Treatment within clinical trials is highly encouraged.*
BSC = best supportive care; CR = complete response; DD-MVAC = dose dense methotrexate vinblastine doxorubicin cisplatin; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PR = partial response; PS = performance status; SD = stable disease.

- Section 7.8 Quality of life, one recommendation was revised based on the new data added.

Summary of evidence	LE
HRQoL data are comparable for robotic radical cystectomy (with either intracorporeal or extracorporeal urinary diversion) and open radical cystectomy.	1b

- Chapter 8 Follow-up; a new section on variant histologies was added.

2. METHODS

2.1 Data identification

For the 2021 MIBC Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the MIBC Guideline was performed. The search was limited to English language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between May 14th, 2020 and June 11th, 2021. A total of 2,290 unique records were identified, retrieved and screened for relevance resulting in 61 new publications having been included in the 2022 print. A detailed search strategy is available online: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=appendices-publications

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [5, 6] which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are grade according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [6]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

The results of a collaborative multi-stakeholder consensus project on the management of advanced and variant BC have been incorporated in the 2020 MIBC Guidelines update [8, 9]. Only statements which reached the *a priori* defined level of agreement - ≥ 70% agreement and ≤ 15% disagreement – across all stakeholders involved in this consensus project are listed. The methodology is presented in detail in the scientific publications. Since the publication of these consensus papers, emerging evidence prompted a re-evaluation of these findings, resulting in the removal of a number of consensus statements.

2.2 Peer-review

The 2021 print of the MIBC Guidelines were peer reviewed prior to publication.

*2.2.1 **Lay review***

Post publication, the 2018 MIBC Guidelines were shared with seven patients treated for MIBC. Their comments were requested, but not limited to:

- the overall tone of the guidelines content;
- any missing information;
- any information considered incorrect;
- any information which is not presented in a clear fashion;
- any text which is considered redundant and should be omitted;
- any text section that should be more detailed.

Common comments across reviewers:

- In general, the overall tone of the text was considered informational and instructive, but the language used obviously targets medical professionals, which make certain parts of the text difficult to understand for lay persons. The use of many abbreviations is considered an additional hindrance, as are the methodological elements. In case the EAU are considering producing a lay version of this text, the language needs to be adapted and clear instructions are to be provided.
- It is difficult for lay reviewers to comment on what may be omitted since, in their opinion, they lack the expertise.

- Some sections, such as 'Recurrent disease' and 'Markers' denote areas where less evidence is available. Consequently, the available data is less systematically presented which makes these sections more difficult to understand.
- There is an interest whether screening for BC is a consideration.
- In particular 'follow-up', 'quality of life' and 'survivorship aspects' should be elaborated on; providing additional information on what may be expected after treatment is considered very helpful for patients and their families. Also lifestyle elements would be of relevance (healthy living, 'what to do to prevent cancer'). For this section, in particular, involvement of patients in the text development was considered missing. Transparency about the process of patient involvement in guidelines development was considered most relevant.

The MIBC Guidelines Panel is most grateful for the unique insights and guidance provided by the lay reviewers.

2.3 Future goals

Topics considered for inclusion in the 2023 update of the MIBC Guidelines:

- a systematic review on the role of Positron Emission Tomography (PET) in the diagnosis and staging of patients presenting with suspected MIBC;
- development of a diagnostic pathway for the assessment of visible and non-visible haematuria;
- participation in developing strategies to ensure meaningful participation of patients in the development and implementation of the MIBC Guidelines.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer is the 7th most commonly diagnosed cancer in males, whilst it drops to 10th position when both genders are considered [10]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 for men and 2.4 for women [10]. In the European Union, the age-standardised incidence rate is 20 for men and 4.6 for women [10]. In Europe, the highest age-standardised incidence rate has been reported in Belgium (31 in men and 6.2 in women) and the lowest in Finland (18.1 in men and 4.3 in women) [10].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.3 for men vs. 0.86 for women in 2012 [10]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, also partly caused by the different methodologies used in the studies and the quality of data collection [11, 12]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [13, 14].

Approximately 75% of patients with BC present with disease confined to the mucosa (stage Ta, carcinoma *in situ* [CIS]) or submucosa (stage T1). In younger patients (< 40 years) this percentage is even higher [15]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality (CSM) compared to T2-4 tumours [10, 11].

3.2 Aetiology

*3.2.1 **Tobacco smoking***

Tobacco smoking is the most well-established risk factor for BC, causing 50–65% of male cases and 20–30% of female cases [16, 17]. A causal relationship has been established between exposure to tobacco and cancer in studies in which chance, bias and confounding can be discounted with reasonable confidence [18].

The incidence of BC is directly related to the duration of smoking and the number of cigarettes smoked per day [19]. A meta-analysis looked at 216 observational studies on cigarette smoking and cancer published between 1961 and 2003, and the pooled risk estimates for BC demonstrated a significant association for both current and former smokers [20]. Recently, an increase in risk estimates for current smokers relative to never smokers has been described suggesting this could be due to changes in cigarette composition [16]. Starting to smoke at a younger age increased the risk of death from BC [21]. An immediate decrease in the risk of BC was observed in those who stopped smoking. The reduction was about 40% within one to four years of quitting smoking and 60% after 25 years of cessation [19]. Encouraging people to stop smoking would result in the incidence of BC decreasing equally in men and women [16].

3.2.2 *Occupational exposure to chemicals*

Occupational exposure is the second most important risk factor for BC. Work-related cases accounted for 20–25% of all BC cases in several series and it is likely to occur in occupations in which dyes (with the exception of hair dyes [22]), rubbers, textiles, paints, leathers, and chemicals are used [23, 24]. The risk of BC due to occupational exposure to carcinogenic aromatic amines is significantly greater after ten years or more of exposure; the mean latency period usually exceeds 30 years [25, 26]. Population-based studies established the occupational attribution for BC in men to be 7.1%, while no such attribution was discernible for women [11, 27].

3.2.3 *Radiotherapy*

Increased rates of secondary bladder malignancies have been reported after external-beam radiotherapy (EBRT) for gynaecological malignancies, with relative risks (RR) of 2–4 [24]. In a population-based cohort study, the standardised incidence ratios for BC developing after radical prostatectomy (RP), EBRT, brachytherapy, and EBRT-brachytherapy were 0.99, 1.42, 1.10, and 1.39, respectively, in comparison with the general U.S. population [28].

It has recently been proposed that patients who have received radiotherapy (RT) for prostate cancer with modern modalities such as intensity-modulated radiotherapy (IMRT) may have lower rates of in-field bladder- and rectal secondary malignancies [29]. Nevertheless, since longer follow-up data are not yet available, and as BC requires a long period to develop, patients treated with radiation and with a long life expectancy are at a higher risk of developing BC [29].

3.2.4 *Dietary factors*

Several dietary factors have been related to BC; however, the links remain controversial. The European Prospective Investigation into Cancer and Nutrition (EPIC) study is an on-going multicentre cohort study designed to examine the association between diet, lifestyle, environmental factors and cancer. They found no links between BC and fluid intake, red meat, vegetable and fruit consumption and only recently an inverse association between dietary intake of flavonoids and lignans and the risk of aggressive BC tumours has been described [30].

3.2.5 *Metabolic disorders*

In a large prospective study pooling six cohorts from Norway, Sweden, and Austria (The Metabolic syndrome and Cancer project, Me-Can 2.0), metabolic aberrations, especially elevated blood pressure and triglycerides, were associated with increased risks of BC among men, whereas high body mass index (BMI) was associated with decreased BC risk. The associations between BMI, blood pressure and BC risk significantly differed between men and women [31].

The association of diabetes mellitus (DM) with the risk of BC has been evaluated in numerous meta-analyses with inconsistent results. When analysing specific subpopulations, DM was associated with BC or CSM risk especially in men [32]. Thiazolidinediones (pioglitazone and rosiglitazone) are oral hypoglycaemic drugs used for the management of type 2 DM. Their use and the association with BC is still a matter of debate. In a recent meta-analysis of observational studies the summary results indicated that pioglitazone use was significantly associated with an increased risk of BC which appears to be linked to higher dose and longer duration of treatment [33]. The U.S. Food and Drug Administration (FDA) recommend that healthcare professionals should not prescribe pioglitazone in patients with active BC [34]. Several countries in Europe have removed this agent from the market or included warnings for prescription. Moreover, the benefits of glycaemic control vs. unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of BC.

3.2.6 *Bladder schistosomiasis and chronic urinary tract infection*

Bladder schistosomiasis (bilharzia) is the second most common parasitic infection after malaria, with about 600 million people exposed to infection in Africa, Asia, South America, and the Caribbean [35]. There is a well-established relationship between schistosomiasis and urothelial carcinoma (UC) of the bladder, which can progress to squamous cell carcinoma (SCC), however, better control of the disease is decreasing the incidence of SCC of the bladder in endemic zones such as Egypt [36, 37].

Similarly, invasive SCC has been linked to the presence of chronic urinary tract infection (UTI) distinct from schistosomiasis. A direct association between BC and UTIs has been observed in several case-control studies, which have reported a two-fold increased risk of BC in patients with recurrent UTIs in some series [38]. However, a recent meta-analysis found no statistical association when pooling data from the most recent and highest quality studies which highlights the need for higher quality data to be able to draw conclusions [39].

Similarly, urinary calculi and chronic irritation or inflammation of the urothelium have been described as possible risk factors for BC. A meta-analysis of case-control and cohort studies suggests a positive association between history of urinary calculi and BC [40].

3.2.7 *Gender*

Although men are more likely to develop BC than women, women present with more advanced disease and have worse survival rates. A meta-analysis including nearly 28,000 patients shows that female gender was associated with a worse survival outcome (hazard ratio [HR]: 1.20, 95% CI: 1.09–1.32) compared to male gender after radical cystectomy (RC) [41]. This finding had already been presented in a descriptive nationwide analysis based on 27,773 Austrian patients. After their analysis the authors found that cancer-specific survival (CSS) was identical for pT1-tumours in both sexes, while women had a worse CSS in both age cohorts (< 70 years and ≥ 70 years) with higher tumour stages [42]. However, treatment patterns are unlikely to explain the differences in overall survival (OS) [43]. In a population-based study from the Ontario Cancer Registry analysing all patients with BC treated with cystectomy or radical RT between 1994 and 2008, no differences in OS, mortality and outcomes were found between males and females following radical therapy [44]. The gender-specific difference in survival for patients with BC was also analysed in the Norwegian population. Survival was inferior for female patients but only within the first 2 years after diagnosis. This discrepancy was partly attributed to a more severe T-stage in female patients at initial diagnoses [45].

A population-based study from the MarketScan databases suggests that a possible reason for worse survival in the female population may be that women experienced longer delays in diagnosis than men, as the differential diagnosis in women includes diseases that are more prevalent than BC [46]. Furthermore, differences in the gender prevalence of BC may be due to other factors besides tobacco and chemical exposure. In a large prospective cohort study, post-menopausal status was associated with an increase in BC risk, even after adjustment for smoking status. This finding suggests that the differences in oestrogen and androgen levels between men and women may be responsible for some of the difference in the gender prevalence of BC [47-49]. Moreover, a recent population study assessing impact of hormones on BC suggests that younger age at menopause (≤ 45 years) is associated with an increased risk of BC [50].

3.2.8 *Genetic factors*

There is growing evidence that genetic susceptibility factors and family association may influence the incidence of BC. A recent population-based study of cancer risk in relatives and spouses of UC patients showed an increased risk for first- and second-degree relatives, and suggests genetic or environmental roots independent of smoking-related behaviour [51]. Shared environmental exposure was recognised as a potentially confounding factor [52]. Recent studies detected genetic susceptibility with independent loci, which are associated with BC risk [53].

Genome-wide association studies (GWAS) of BC identified several susceptibility loci associated with BC risk [54, 55].

3.2.9 *Summary of evidence and guidelines for epidemiology and risk factors*

Summary of evidence	**LE**
Worldwide, bladder cancer is the 10th most commonly diagnosed cancer.	2a
Several risk factors associated with BC diagnosis have been identified.	3
Active and passive tobacco smoking continues to be the main risk factor, while exposure-related incidence is decreasing.	2a
The increased risk of developing BC in patients undergoing EBRT, brachytherapy, or a combination of EBRT and brachytherapy, must be considered during patient follow-up. As BC requires time to develop, patients treated with radiation at a young age are at the greatest risk and should be followed-up closely.	3

Recommendations	**Strength rating**
Council patients to stop active and avoid passive smoking.	Strong
Inform workers in potentially hazardous workplaces of the potential carcinogenic effects of a number of recognised substances, including duration of exposure and latency periods. Protective measures are recommended.	Strong
Do not prescribe pioglitazone to patients with active bladder cancer or a history of bladder cancer.	Strong

3.3 Pathology

3.3.1 Handling of transurethral resection and cystectomy specimens

During transurethral resection (TUR), a specimen from the tumour and normal looking bladder wall should be taken, if possible. Specimens should be taken from the superficial and deep areas of the tumour and sent to the pathology laboratory separately, in case the outcome will impact on treatment decisions. If random biopsies of the flat mucosa are taken, each biopsy specimen of the flat mucosa should also be submitted separately [56]. The sampling sites must be recorded by the urologist; the pathologist report should include location of tumour tissue in the cystectomy specimen. Anatomical tumour location is relevant for staging and prognosis [57, 58].

In RC, bladder fixation must be carried out as soon as possible. The pathologist must open the specimen from the urethra to the bladder dome and fix the specimen. In a female cystectomy specimen, the length of the urethral segment removed *en bloc* with the specimen should be checked, preferably by the urological surgeon [59].

Specimen handling should follow the general rules as published by a collaborative group of pathologists and urologists [60, 61]. It must be stressed that it may be very difficult to confirm the presence of a neoplastic lesion using gross examination of the cystectomy specimen after TUR or chemotherapy, so the entire retracted or ulcerated area should be included.

It is compulsory to study the urethra, the ureters, the prostate in men and the radial margins [62]. In urethra-sparing cystectomy; the level of urethral dissection, completeness of the prostate, specifically at the apex (in men), and the inclusion of the entire bladder neck and amount of adjacent urethra, uterus and vaginal vault (in women) have to be documented by the pathologist.

All lymph node (LN) specimens should be provided in their totality, in clearly labelled containers. In case of doubt or adipose differentiation of the LNs, the entire specimen is to be included. Lymph nodes should be counted and measured on slides; capsular extension and percentage of LN invasion should be reported as well as vascular embols [63, 64]. In case of metastatic spread in the perivesical fat without real LN structures (capsule, subcapsular sinus), this localisation should nevertheless be considered as N+. Potentially positive soft tissue margins should be inked by the pathologist for evaluation [65]. In rare cases, fresh frozen sections may be helpful to determine treatment strategy [66].

3.3.2 Pathology of muscle-invasive bladder cancer

All MIBC cases are high-grade UCs. For this reason, no prognostic information can be provided by grading MIBC [67]. However, identification of morphological subtypes is important for prognostic reasons and treatment decisions [68-70].

The data presented in these guidelines are based on the 2004/2016 World Health Organization (WHO) classifications [71, 72].

Currently the following differentiations are used [68, 73]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic divergent differentiation;
3. micropapillary UC;
4. nested variant (including large nested variant) and microcystic UC;
5. plasmacytoid, giant cell, signet ring, diffuse, undifferentiated;
6. lymphoepithelioma-like;
7. small-cell carcinomas;
8. sarcomatoid UC;
9. neuroendocrine variant of UC;
10. some UCs with other rare differentiations.

Outcomes may vary for divergent histologies, which need to be mentioned following international reporting standards [68, 74].

3.3.3 *Guidelines for the assessment of tumour specimens*

Recommendations	Strength rating
Record the depth of invasion (categories pT2a and pT2b, pT3a and pT3b or pT4a and pT4b).	Strong
Record margins with special attention paid to the radial margin, prostate, ureter, urethra, peritoneal fat, uterus and vaginal vault.	
Record the total number of lymph nodes (LNs), the number of positive LNs and extranodal spread.	
Record lymphovascular invasion.	
Record the presence of carcinoma *in situ*.	
Record the sampling sites as well as information on tumour size when providing specimens to the pathologist.	

3.3.4 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer* [8, 9]*

Consensus statement
Bladder UC with small cell neuroendocrine variant should be treated with neoadjuvant chemotherapy followed by consolidating local therapy.
Muscle-invasive pure squamous cell carcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive pure adenocarcinoma of the bladder should be treated with primary radical cystectomy and lymphadenectomy.
Muscle-invasive small cell neuroendocrine variant of bladder UC should not receive preventive brain irradiation to avoid brain recurrence.
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.
T1 high-grade bladder urothelial cancer with micropapillary histology (established after complete TURBT and/or re-TURBT) should be treated with immediate radical cystectomy and lymphadenectomy.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Pathological staging

For staging, the Tumour, Node, Metastasis (TNM) Classification (2017, 8th edition) is recommended [75]. Blood and lymphatic vessel invasion have an independent prognostic significance [76, 77].

4.2 Tumour, node, metastasis classification

The TNM classification of malignant tumours is the method most widely used to classify the extent of cancer spread [75] (Table 4.1).

Table 4.1: TNM Classification of urinary bladder cancer [75]

T - Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
T3a	microscopically
T3b	macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis	
M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastasis

Staging after neoadjuvant chemotherapy (NAC) and RC can be done, but must be mentioned as ypTNM (International Collaboration on Cancer Reporting) [74]. ypT0N0 after NAC and cystectomy is associated with good prognosis [78, 79].

5. DIAGNOSTIC EVALUATION

5.1 Primary diagnosis

*5.1.1 **Symptoms***

Painless visible haematuria is the most common presenting complaint. Other presenting symptoms and clinical signs include non-visible haematuria, urgency, dysuria, increased frequency, and in more advanced tumours, pelvic pain and symptoms related to urinary tract obstruction.

*5.1.2 **Physical examination***

Physical examination should include rectal and vaginal bimanual palpation. A palpable pelvic mass can be found in patients with locally advanced tumours. In addition, bimanual examination under anaesthesia should be carried out before and after TUR of the bladder (TURB) to assess whether there is a palpable mass or if the tumour is fixed to the pelvic wall [80, 81]. However, considering the discrepancy between bimanual examination and pT stage after cystectomy (11% clinical overstaging and 31% clinical understaging), some caution is suggested with the interpretation of bimanual examination [82].

*5.1.3 **Bladder imaging***

Patients with a bladder mass identified by any diagnostic imaging technique should undergo cystoscopy, biopsy and/or resection for histopathological diagnosis and staging.

The high specificity of diagnostic imaging for detecting BC means that patients with imaging positive for BC may avoid diagnostic flexible cystoscopy and go directly to rigid cystoscopy and transurethral resection [83, 84].

5.1.4 *Urinary cytology*

Examination of voided urine or bladder washings for exfoliated cancer cells has high sensitivity in high-grade tumours and is a useful indicator in cases of high-grade malignancy or CIS. However, positive urinary cytology may originate from a urothelial tumour located anywhere in the urinary tract.

Evaluation of cytology specimens can be hampered by low cellular yield, UTIs, stones or intravesical instillations, but for experienced readers, specificity exceeds 90% [85, 86]. However, negative cytology does not exclude a tumour. There is no known urinary marker specific for the diagnosis of invasive BC [87].

A standardised reporting system, the 'Paris System' redefining urinary cytology diagnostic categories was published in 2016 [88]:

- adequacy of urine specimens (Adequacy);
- negative for high-grade UC (Negative);
- atypical urothelial cells (AUC);
- suspicious for high-grade UC (Suspicious);
- high-grade UC (HGUC);
- low-grade urothelial neoplasia (LGUN).

5.1.5 *Cystoscopy*

Ultimately, the diagnosis of BC is made by cystoscopy and histological evaluation of resected tissue. An (outpatient) flexible cystoscopy is recommended to obtain a complete image of the bladder. However, in daily practice, If a bladder tumour has been visualised unequivocally by imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US), diagnostic cystoscopy may be omitted and the patient can proceed directly to TURB for histological diagnosis and resection. During the procedure, a thorough investigation of the bladder with rigid cystoscopy under anaesthesia is mandatory in order not to miss any tumours at the level of the bladder neck. Currently, there is no evidence for the role of photodynamic diagnosis (PDD) in the standard diagnosis of invasive BC.

A careful description of the cystoscopic findings is necessary. This should include documentation of the site, size, number, and appearance (papillary or solid) of the tumours, as well as a description of any mucosal abnormalities [89]. The use of a bladder diagram is recommended.

The use of PDD could be considered if a T1 high-grade tumour is present and to identify associated CIS. Presence of CIS may lead to a modified treatment plan (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]). Photodynamic diagnosis is highly sensitive for the detection of CIS and in experienced hands the rate of false-positive results may be similar to that with regular white-light cystoscopy [77, 90].

5.1.6 *Transurethral resection of invasive bladder tumours*

The goal of TURB is to enable histopathological diagnosis and staging, which requires the inclusion of bladder muscle in the resection specimen.

In case MIBC is suspected, tumours need to be resected separately in parts, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labelled container to enable making a correct diagnosis. In cases in which RT is considered and CIS is to be excluded, PDD can be used [91].

The involvement of the prostatic urethra and ducts in men with bladder tumours has been reported. The exact risk is not known, but it seems to be higher if the tumour is located on the trigone or bladder neck, with concomitant bladder CIS, and in the case of multiple tumours [58, 92, 93]. Involvement of the prostatic urethra can be determined either at the time of primary TURB or by frozen section during the cystoprostatectomy procedure. A frozen section has a higher negative-predictive value and is more accurate [94-96].

A negative urethral frozen section can reliably identify patients in whom urethrectomy should be avoided. However, a positive pre-operative biopsy seems to have limited utility as these findings are not reliably associated with final margin status [94, 97].

Diagnosis of a urethral tumour before cystectomy will result in a urethrectomy which could be a contraindication for an orthotopic diversion. However, an orthotopic diversion should not be denied based on positive pre-operative biopsy findings alone and frozen section should be part of the RC procedure, in particular in male patients [98, 99].

5.1.7 *Summary of evidence and guidelines for the primary assessment of presumably invasive bladder tumours*

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of bladder cancer.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*.	2b
In men, prostatic urethral biopsy includes resection from the bladder neck to the verumontanum (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	2b

Recommendations	Strength rating
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma *in situ* is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	Strong
In men with a negative prostatic urethral biopsy undergoing subsequent orthotopic neobladder construction, an intra-operative frozen section can be omitted.	Strong
In men with a prior positive transurethral prostatic biopsy, subsequent orthotopic neobladder construction should not be denied a priori, unless an intra-operative frozen section of the distal urethral stump reveals malignancy at the level of urethral dissection.	Strong
In women undergoing subsequent orthotopic neobladder construction, obtain procedural information (including histological evaluation) of the bladder neck and urethral margin, either prior to, or at the time of cystectomy.	Strong
In the pathology report, specify the grade, depth of tumour invasion, and whether the lamina propria and muscle tissue are present in the specimen.	Strong

(For general information on the assessment of bladder tumours, see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2])

5.1.8 *EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

Consensus statement
Differentiating between urachal and non-urachal subtypes of adenocarcinoma is essential when making treatment decisions.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

5.2 Imaging for staging of MIBC

In clinical practice, tumour stage and histopathological grade are used to guide treatment and determine prognosis [73, 100, 101]. In symtomatic and high-risk patients imaging is used to assess bladder abnormalities. In addition, imaging is increasingly becoming an essential investigation for local- and distant staging of BC.

The goal of imaging patients with BC is to:

- detect lesions (US when applicable);
- differentiate T1 from T2 tumours as their treatment will differ (MRI using the Vesical Imaging Reporting and Data System [VI-RADS] score);
- Evaluate the extent of locally advanced tumour stage or tumour spread to LNs (CT scan and MRI for abdominal- and pelvic LNs or PET/CT scan);
- assess tumour spread to the upper UT or other distant organs (e.g., liver, lungs, bones, peritoneum, pleura, and adrenal glands) (CT urography for evaluating the UUT and PET/CT to detect distant organs metastasis).

Staging must be accurate to allow for the most optimal treatment choice.

5.2.1 ***Local staging of MIBC***

5.2.1.1 *Magnetic resonance imaging for local staging of MIBC*

Magnetic resonance imaging has superior soft tissue contrast resolution compared with CT and can evaluate post-biopsy reaction as enhancement of the tumour occurs earlier than that of the normal bladder wall due to neovascularisation [102, 103].

The accuracy of MRI for primary tumour staging varies from 73% to 96% (mean 85%). Huang *et al.*, in a systematic review, showed a pooled sensitivity and specificity of 0.90 and 0.88, respectively, with results going up to 0.92 and 0.96 when MRI was performed with a 3T scan, with diffusion-weighted magnetic resonance imaging (DWI) as part of the acquisition protocol [104]. A systematic review evaluating 20 studies (n = 1,724), showed a pooled sensitivity and specificity for differentiating between stages ≤ T1 and ≥ T2 of 0.92 (95% CI: 0.88–0.95) and 0.88 (95% CI: 0.78–0.94), respectively [105]. Considering the link established between the use of gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF), in patients with impaired renal function contrast medium should be managed according to the European Society of Urogenital Radiology (ESUR) Guidelines [106].

More recently, multiparametric (mp) MRI using the VI-RADS scoring system has been introduced which proved to be able to differentiate between muscle- and non-muscle-invasive primary BC (T1 vs. T2 tumours) with high diagnostic accuracy [107]. The VI-RADS offers a standardised approach to both acquisition and reporting of mpMRI for BC, however, the best use of mpMRI in this setting and which cut-off levels are to be used for VI-RADS scoring still need to be determined [103]. To date, the VI-RADS score has been validated by several research groups, showing good diagnostic performance in detecting MIBC [108, 109].

A meta-analysis found that the pooled sensitivity and specificity of mpMRI with VI-RADS acquisition and scoring for predicting MIBC were 0.83 and 0.90, respectively. The diagnostic performance of VI-RADS is similar to the diagnostic performance of bladder MRI in determining MIBC based on a previous meta-analysis of 24 studies in which the pooled sensitivity and specificity were 0.92 (95% CI: 0.88–0.95) and 0.87 (95% CI: 0.78–0.93), respectively [110]. The analysis found substantial inter-reader agreement, with kappa (κ) values ranging from 0.81 to 0.92 [110]. A systematic review and meta-analysis (n = 1,016) showed a pooled weighted mean κ estimate of 0.83 (95% CI: 0.78–0.88) [111].

5.2.1.2 *CT imaging for local staging of MIBC*

The advantages of CT include high spatial resolution, shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to variable patient factors. Computed tomography is unable to differentiate between stages Ta to T3a tumours, but it is useful for detecting invasion into the perivesical fat (T3b) and adjacent organs. The accuracy of CT in determining extravesical tumour extension varies from 55% to 92% [112] and increases with more advanced disease [113].

Both CT and MRI may be used for assessment of local invasion by T3b disease, or higher, but they are unable to accurately diagnose microscopic invasion of perivesical fat (T2 vs. T3a) [114]. Contrast-enhanced CT using iodinated contrast media can be considered as an alternative to MRI when MRI is contraindicated [115].

5.2.2 ***Imaging of lymph nodes in MIBC***

Assessment of LN metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally-enlarged nodes. The sensitivity for detection of LN metastases is low (48–87%). Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours [116-120]. Pelvic nodes > 8 mm and abdominal nodes > 10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged [121, 122].

Positron emission tomography (PET) combined with CT is increasingly being used in clinical practice and its exact role continues to be evaluated [123].

5.2.3 ***Upper urinary tract urothelial carcinoma***

5.2.3.1 *Computed tomography urography*

Computed tomography urography has the highest diagnostic accuracy of the available imaging techniques [124]. The sensitivity of CT urography for UTUC is 0.67–1.0 and specificity is 0.93–0.99 [125].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial ‘flat lesions’ without mass effect or urothelial thickening are generally not visible with CT.

The secondary sign of hydronephrosis is associated with advanced disease and poor oncological outcome [126, 127]. The presence of enlarged LNs is highly predictive of metastases in UTUC [128].

5.2.3.2 *Magnetic resonance urography*

Magnetic resonance urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [129]. The sensitivity of MR urography is 0.75 after contrast injection for tumours < 2 cm [129]. The use of MR urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of NSF. Computed tomography urography is generally preferred to MR urography for diagnosing and staging UTUC.

5.2.4 ***Distant metastases at sites other than lymph nodes***

Prior to any curative treatment, it is essential to evaluate the presence of distant metastases. Computed tomography and MRI are the diagnostic techniques of choice to detect lung [130] and liver metastases [131], respectively. Bone and brain metastases are rare at the time of presentation of invasive BC. A bone scan and additional brain imaging are therefore not routinely indicated unless the patient has specific symptoms or signs to suggest bone or brain metastases [132, 133]. Magnetic resonance imaging is more sensitive and specific for diagnosing bone metastases than bone scintigraphy [134, 135].

5.2.5 ***Future developments***

Evidence is accruing in the literature suggesting that ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT might have potential clinical use for staging metastatic BC [136, 137], but results of further trials are awaited before a recommendation can be made. The potential role of mpMRI as first-line test for local staging of BC rather than TURB has been demonstrated in a recent clinical trial [138].

Future trends might include image analysis radiomic-based techniques in predicting MIBC. A meta-analysis (n = 860) provided summary estimates for sensitivity and specificity in predicting MIBC of 82% (95% CI: 77–86%) and 81% (95% CI: 76–85%), respectively [139].

A clinical trial assessed the role of PET/CT in evaluating LN involvement in patients receiving neoadjuvant pembrolizumab. The performance of PET/CT did not justify its routine use in cN0 MIBC patients, but proved useful in optimising selection of MIBC patients suited for neoadjuvant immunotherapy strategies in a clinical trial setting [140].

The first study evaluating the performance of MRI in assessing therapeutic response to induction chemotherapy showed superiority of DWI over T2-weighted and dynamic contrast-enhanced (DCE)-MRI [141]. The high specificity of DWI indicates that it is useful for accurate prediction of a complete histopathological response, allowing better patient selection for bladder-sparing protocols. Pre-operative MRI in different settings may provide useful information regarding treatment response. Potential future application of the VI-RADS score may include prediction of therapy response as well as peri-operative outcomes [142].

5.2.6 ***Summary of evidence and guidelines for staging in muscle-invasive bladder cancer***

Summary of evidence	**LE**
Imaging as part of staging in muscle-invasive bladder cancer (MIBC) provides information about prognosis and assists in selection of the most appropriate treatment.	2b
The diagnosis of upper tract UC depends on CT urography and ureteroscopy.	2b
In local staging, MRI is superior to CT in terms of differentiating T1 from T2 disease.	2b

Recommendations	**Strength rating**
In patients with confirmed muscle-invasive bladder cancer, use computed tomography (CT) of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation.	Strong
Use CT urography, unless it is contraindicated for reasons related to contrast administration or radiation dose; in that case use magnetic resonance imaging.	Strong

5.3 MIBC and health status

Complications from RC may be directly related to pre-existing comorbidity as well as the surgical procedure, bowel anastomosis, or urinary diversion. A significant body of literature has evaluated the usefulness of age as a prognostic factor for RC, although chronological age is less important than frailty [143-145]. Frailty is a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and

negative side effects of cancer treatment [146]. Controversy remains regarding age, RC and the type of urinary diversion. Radical cystectomy is associated with the greatest risk reduction in disease-related and non-disease-related death in patients aged < 80 years [147].

The largest retrospective study on RC in septuagenarians and octogenarians based on data from the National Surgical Quality Improvement Program database (n = 1,710) showed no significant difference for wound, cardiac, or pulmonary complications. However, the risk of mortality in octogenarians compared to septuagenarians is higher (4.3% vs. 2.3%) [148]. Although some octogenarians successfully underwent a neobladder procedure, most patients were treated with an ileal conduit diversion. It is important to evaluate functioning and quality of life (QoL) of older patients using a standardised geriatric assessment, as well as carrying out a standard medical evaluation [149].

Sarcopenia has been shown to be an independent predictor for OS and CSS in a large multicentre study with patients undergoing RC for BC [150]. In order to predict CSM after RC in patients receiving neoadjuvant chemotherapy (NAC), sarcopenia should be assessed after completing the chemotherapy [151]. Other risk factors for morbidity include prior abdominal surgery, extravesical disease, and prior RT [152]. Female gender, an increased BMI and lower pre-operative albumin levels are associated with a higher rate of parastomal hernias [153]. Low pre-operative serum albumin is also associated with impaired wound healing, gastrointestinal (GI) complications and a decrease of recurrence-free and OS after RC [154, 155]. Therefore, it could be used as a prognostic biomarker for patients undergoing RC.

*5.3.1 **Evaluation of comorbidity, frailty and cognition***

Rochon *et al.*, have shown that evaluation of comorbidity provides a better indicator of life expectancy in MIBC than patient age [156]. Evaluation of comorbidity helps to identify factors likely to interfere with, or have an impact on, treatment and the evolution and prognosis of MIBC [157].

The value of assessing overall health before recommending and proceeding with surgery was emphasised by Zietman *et al.*, who have demonstrated an association between comorbidity and adverse pathological and survival outcomes following RC [158]. Similar results were found for the impact of comorbidity on cancer-specific and other-cause mortality in a population-based competing risk analysis of > 11,260 patients from the Surveillance, Epidemiology, and End Results (SEER) registries. Age carried the highest risk for other-cause mortality but not for increased cancer-specific death, while the stage of locally advanced tumour was the strongest predictor for decreased CSS [159].

Stratifying older patients according to frailty using a multidisciplinary approach will help select patients most likely to benefit from radical surgery and to optimise treatment outcomes [160]. There are many different screening tools available for frailty and local approaches can be used. Examples include the G8 and the Clinical Frailty Scale (See Table 5.1 and Figure 5.1 below).

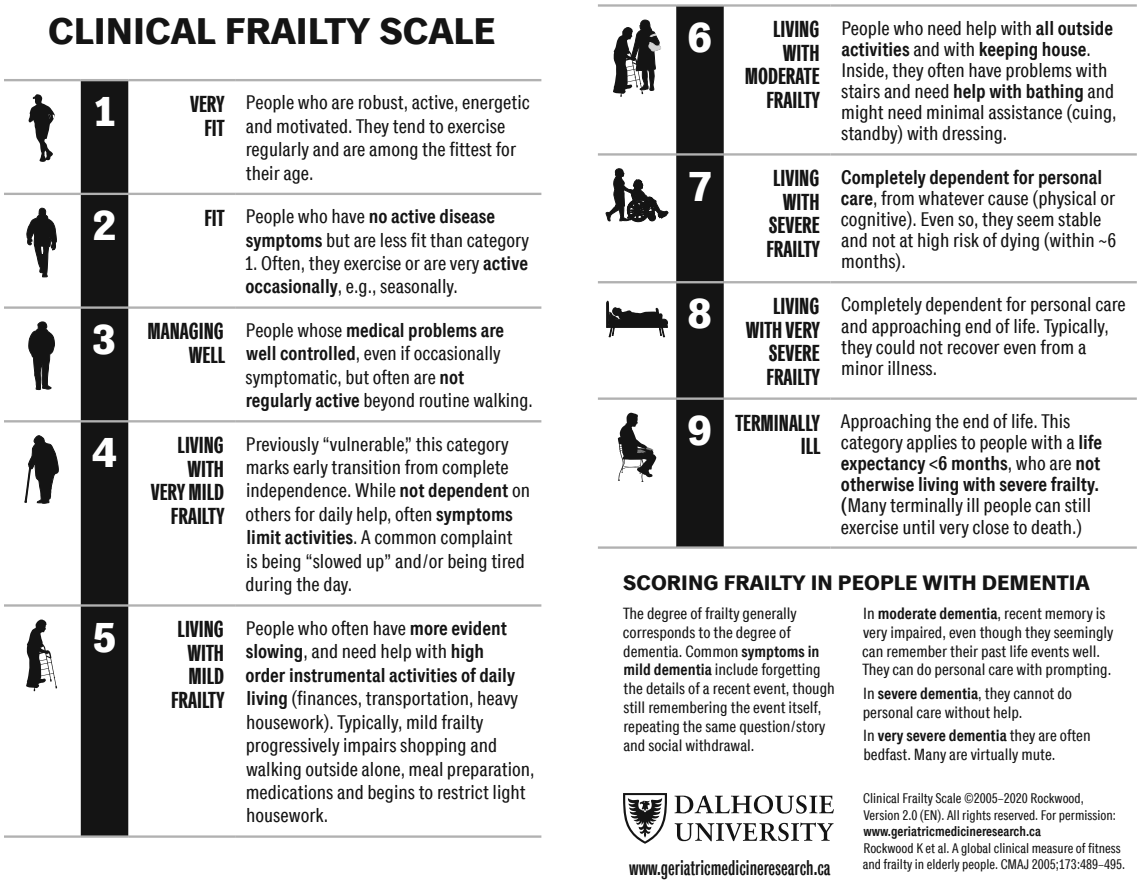
Cognitive impairment can be screened for using a tool such as the mini-COG (https://mini-cog.com/), which consists of three-word recall and a clock-drawing test, and can be completed within 5 minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g., Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an important factor in health status assessment. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [161].

Table 5.1: G8 screening tool (adapted from [162])

	Items	Possible responses (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last 3 months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed or chair bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems

E	BMI? (weight in kg)/(height in m^2)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80–85
		2 = < 80
	Total score	**0–17**

Figure 5.1: Clinical Frailty Scale©, Version 2.0* [163]


CLINICAL FRAILTY SCALE
1 VERY FIT
People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
2 FIT
People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.
3 MANAGING WELL
People whose medical problems are well controlled, even if occasionally symptomatic, but often are not regularly active beyond routine walking.
4 LIVING WITH VERY MILD FRAILTY
Previously "vulnerable," this category marks early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up" and/or being tired during the day.
5 LIVING WITH MILD FRAILTY
People who often have more evident slowing, and need help with high order instrumental activities of daily living (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
6 LIVING WITH MODERATE FRAILTY
People who need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
7 LIVING WITH SEVERE FRAILTY
Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
8 LIVING WITH VERY SEVERE FRAILTY
Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
9 TERMINALLY ILL
Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death.)
SCORING FRAILTY IN PEOPLE WITH DEMENTIA
The degree of frailty generally corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.
In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
In severe dementia, they cannot do personal care without help.
In very severe dementia they are often bedfast. Many are virtually mute.
DALHOUSIE UNIVERSITY
www.geriatricmedicineresearch.ca
Clinical Frailty Scale ©2005–2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: www.geriatricmedicineresearch.ca
Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.

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5.3.2 Comorbidity scales, anaesthetic risk classification and geriatric assessment

A range of comorbidity scales has been developed [164], seven of which have been validated [165-171]. The Charlson Comorbidity Index (CCI) ranges from 0 to 30 according to the importance of comorbidity described at four levels and is calculated by healthcare practitioners based on patients' medical records. The score has been widely studied in patients with BC and found to be an independent prognostic factor for peri-operative mortality [172, 173], overall mortality [174], and CSM [147, 175-177]. Only the age-adjusted version of the CCI was correlated with both cancer-specific and other-cause mortality [178]. The age-adjusted CCI (Table 5.2) is the most widely used comorbidity index in cancer for estimating long-term survival and is easily calculated [179].

Health assessment of oncology patients must be supplemented by measuring their activity level. Extermann *et al.*, have shown that there is no correlation between morbidity and competitive activity level [180]. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores and Karnofsky index have been

validated to measure patient activity [181]. Performance score is correlated with patient OS after RC [176] and palliative chemotherapy [182-184].

Patients who have screened positive for frailty or cognitive impairment benefit from an assessment by a geriatrician. This allows identification of geriatric syndromes and any scope for optimisation. The most complete protocol is the Comprehensive Geriatric Assessment (CGA) [185] which is useful in the care of cancer patients [186]. In BC, the CGA has been used to adapt gemcitabine chemotherapy in previously untreated older patients with advanced BC [187].

Table 5.2: Calculation of the Charlson Comorbidity Index

Number of points	Conditions
1	50–60 years
	Myocardial infarction
	Heart failure
	Peripheral vascular insufficiency
	Cerebrovascular disease
	Dementia
	Chronic lung disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	61–70 years
	Hemiplegia
	Moderate to severe kidney disease
	Diabetes with organ damage
	Tumours of all origins
3	71–80 years
	Moderate to severe liver disease
4	81–z years
5	> 90 years
6	Metastatic solid tumours
	AIDS

Interpretation:
1. Calculate Charlson Comorbidity Score or Index = i
    a. Add comorbidity score to age score
    b. Total denoted as 'i' in the Charlson Probability calculation (see below).
    i = sum of comorbidity score to age score
2. Calculate Charlson Probability (10-year mortality = Y)
    a. Calculate $Y = 10^{(i \times 0.9)}$
    b. Calculate $\bar{Z} = 0.983^{Y}$ (where $\bar{Z}$ is the 10-year survival)

5.3.3 Summary of evidence and guidelines for comorbidity scales

Summary of evidence	LE
Chronological age is of limited relevance.	3
It is important to screen for frailty and cognitive impairment and provide a Comprehensive Geriatric Assessment (CGA) where optimisation is needed.	3

Recommendations	Strength rating
Base the decision on bladder-sparing treatment or radical cystectomy in older/frail patients with invasive bladder cancer on tumour stage and frailty.	Strong
Assess comorbidity by a validated score, such as the Charlson Comorbidity Index. The American Society of Anesthesiologists score should not be used in this setting (see Section 5.3.2).	Strong

6. MARKERS

6.1 Introduction

Both patient and tumour characteristics guide treatment decisions and prognosis of patients with MIBC.

6.2 Prognostic markers

*6.2.1 **Histopathological and clinical markers***

The most important histopathological prognostic variables after RC and LN dissection are tumour stage and LN status [188]. In addition, other histopathological parameters of the RC specimen have been associated with prognosis.

The value of lymphovascular invasion was reported in a systematic review and meta-analysis including 78,000 patients from 65 studies treated with RC for BC [189]. Lymphovascular invasion was present in 35% of the patients and correlated with a 1.5-fold higher risk of recurrence and CSM, independent of pathological stage and peri-operative chemotherapy. This correlation was even stronger in those patients with node-negative disease [190].

In a systematic review and meta-analysis including 23 studies and over 20,000 patients, the presence of concomitant CIS in the RC specimen was associated with a higher odds ratio (OR) of ureteral involvement (pooled OR: 4.51, 2.59–7.84). Concomitant CIS was not independently associated with OS, recurrence-free survival (RFS) and DSS in all patients, but in patients with organ-confined disease concomitant CIS was associated with worse RFS (pooled HR: 1.57; 1.12–2.21) and CSM (pooled HR: 1.51, 1.001–2.280) [190].

Tumour location has been associated with prognosis. Tumours located at the bladder neck or trigone of the bladder appear to have an increased likelihood of nodal metastasis (OR: 1.83, 95% CI: 1.11–2.99) and have been associated with decreased survival [188, 191-193].

Prostatic urethral involvement at the time of RC was also found to be associated with worse survival outcomes. In a series of 995 patients, prostatic involvement was recorded in 31% of patients. The 5-year CSS in patients with CIS of the prostatic urethra was 40%, whilst the prognosis of patients with UC invading the prostatic stroma was worse with a 5-year CSS of only 12% [194].

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a prognostic factor in UUT tumours [1] and other non-urological malignancies. In a pooled analysis of 21 studies analysing the prognostic role of NLR in BC, the authors correlated elevated pre-treatment NLR with OS, RFS and disease-free survival (DFS) in both localised and metastatic disease [195]. In contrast, a secondary analysis of the Southwest Oncology Group (SWOG) 8710 trial, a randomised phase III trial assessing cystectomy ± NAC in patients with MIBC, suggests that NLR is neither a prognostic nor a predictive biomarker for OS in MIBCs [196].

In patients with LN-positive disease, the American Joint Committee on Cancer (AJCC)-TNM staging system provides 3 subcategories. In addition, several other prognostic LN-related parameters have been reported. These include, but are not limited to, the number of positive LNs, the number of LNs removed, LN density (the ratio of positive LNs to the number of LNs removed) and extranodal extension. In a systematic review and meta-analysis, it was reported that LN density was independently associated with OS (HR: 1.45, 95%, CI: 1.11–1.90) [197]. It has been suggested that LN density outperforms the AJCC-TNM staging system for LN-positive disease in terms of prognostic value [198, 199]. However, in spite of these studies supporting the use of LN density, LN density relies on the number of LNs removed which, in turn, is subject to surgical and pathological factors. This makes the concept of LN density difficult to apply uniformly [200].

Two studies investigated whether any of the reported LN-related parameters may be superior to the routinely used AJCC-TNM staging system [200, 201]. Whilst the conclusion was that the AJCC-TNM staging system for LN status did not perform well, none of the other tested variables outperformed the AJCC system.

*6.2.2 **Molecular markers***

6.2.2.1 Molecular subtypes based on the Cancer Genome Atlas cohort

The updated Cancer Genome Atlas (TCGA) reported on 412 MIBCs and identified two main groups; luminal and basal-squamous - consisting of five mRNA expression-based molecular subtypes including luminal-papillary, luminal-infiltrated, luminal; basal-squamous; and neuronal, a subtype associated with poor survival in which the majority of tumours do not have small cell or neuroendocrine histology. Each subtype is associated with distinct mutational profiles, histopathological features and prognostic and treatment implications [202].

The basal-squamous subtype is characterised by expression of basal keratin markers, immune infiltrates and is felt to be chemosensitive. The different luminal subtypes are characterised by fibroblast growth factor receptor 3 (*FGFR3*) alterations (luminal-papillary [LumP]), epithelial-mesenchymal transition (EMT) markers (luminal-infiltrated) and may be associated with chemotherapy resistance [69, 70, 202, 203].

In 2019, a consensus on molecular subtype classification was reported [204]. The authors analysed 1,750 MIBC transcriptomic profiles from 18 datasets and identified six MIBC molecular classes that reconcile all previously published classification schemes. The molecular subgroup classes include LumP, luminal non-specified (LumNS), luminal unstable (LumU), stroma-rich, basal/squamous (Ba/Sq), and neuroendocrine-like (NE-like). Each class has distinct differentiation patterns, oncogenic mechanisms, tumour micro-environments and histological and clinical associations. However, the authors stressed that consensus was reached for biological rather than clinical classes. Therefore, at this time, the classification should be considered as a research tool for retrospective and prospective studies until future studies establish how these molecular subgroups can be used best in a clinical setting.

Molecular classification of MIBC is still evolving and treatment tailored to molecular subtype is not a standard yet. A novel 12-gene signature derived from patients in the TCGA utilising published gene signatures has been developed and externally validated to predict OS in MIBC [205]. Interestingly, a recently published analysis of molecular subtyping in MIBC demonstrated that although molecular subtypes reflect the heterogeneity of bladder tumours and are associated with tumour grade, clinical parameters outperformed subtypes for predicting outcome [206]. In the coming years, new insights into BC carcinogenesis may change our management of the disease and our ability to better predict outcomes [207]. Outside clinical trials, molecular subtyping, either by expression profiling or immunohistochemistry, is not yet part of routine clinical work-up awaiting more conclusive data.

6.3 *Predictive markers*

6.3.1 Clinical and histopathological markers

Based on retrospective data only, patients with secondary MIBC have a worse response to NAC compared to patients with primary MIBC [208]. Pietzak *et al.*, retrospectively analysed clinico-pathologic outcomes comparing 245 patients with clinical T2–4a N0M0 primary MIBC and 43 patients with secondary MIBC treated with NAC and RC. They found that patients with secondary MIBC had lower pathologic response rates following NAC than those with primary MIBC (univariable 26% vs. 45%, multivariable OR: 0.4 [95% CI: 0.18–0.84, p = 0.02]). They also found that MIBC patients progressing after NAC had worse CSS as compared to patients treated with cystectomy alone (p = 0.002).

Variant histologies and non-UC have also been linked to worse outcomes after NAC, but there is, as yet, insufficient data to conclude that they can be considered as predictive markers [209].

6.3.2 Molecular markers

Several predictive biomarkers have been investigated such as serum vascular endothelial growth factor [210], circulating tumour cells as well as defects in DNA damage repair (DDR) genes including *ERCC2, ATM, RB1* and *FANCC* that may predict response to cisplatin-based NAC [211, 212]. More recently, alterations in *FGFR3* including both mutations and gene fusions have been shown to be associated with response to *FGFR* inhibitors [213, 214].

More recent efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 (PD-L1) expression by immunohistochemistry has been evaluated in several studies with mixed results which may in part be related to the use of different antibodies and various scoring systems evaluating different compartments, i.e., tumour cells, immune cells, or both. The major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. For example, in the IMvigor 210 phase II study of atezolizumab in patients with advanced/metastatic UC who progressed after platinum-based chemotherapy, responses were seen in 18% of patients with low/no PD-L1 expression [215]. At present, the only indication for PD-L1 testing relates to the use of immune checkpoint inhibitors as monotherapy in patients with locally advanced or metastatic UC unfit for cisplatin-containing chemotherapy who have not received prior therapy. In this setting, atezolizumab (approved by the FDA and EMA) or pembrolizumab (EMA approval only) should only be used in patients unfit for cisplatin-containing chemotherapy whose tumours overexpress PD-L1 (i.e., in case of atezolizumab; tumour-infiltrating immune cells [IC] covering ≥ 5% of the tumour area using the SP142 assay; in case of pembrolizumab, a combined positive score (CPS) of ≥ 10 using the Dako 22C33 platform) [216]. The FDA revised the label for pembrolizumab in patients with advanced UC with approval in first line only for patients not eligible for any platinum-based chemotherapy, however, irrespective of PD-L1 status.

Urothelial cancer is associated with a high tumour mutational burden (TMB) [217]. Both predicted neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic BC [215, 218]. Conflicting results have been seen in studies evaluating immune checkpoint inhibitors in the neoadjuvant setting with the Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With

Muscle-Invasive Urothelial Bladder Carcinoma (PURE)-01 study utilising pembrolizumab demonstrating an association of high TMB with response while there was no association with atezolizumab in the Phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in MIBC (ABACUS) [219, 220].

Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes as discussed earlier, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of transforming growth factors (TGFs) in predicting response to immune checkpoint blockade [221, 222]. Most recently, Powles *et al.*, have reported on the potential for ctDNA to guide the use of adjuvant immunotherapy (IO) in UC [223]. In 581 patients from a phase III RCT of adjuvant atezolizumab vs. observation in UC, ctDNA testing at the start of therapy identified 214 (37%) patients who were positive for ctDNA and who had poor prognosis (observation arm HR = 6.3, 95% CI: 4.45–8.92; p < 0.0001). Patients who were positive for ctDNA had improved DFS and OS in the atezolizumab arm vs. the observation arm (DFS HR = 0.58 [95% CI: 0.43–0.79]; p = 0.0024, OS HR = 0.59 [95% CI: 0.41–0.86]). There was no difference in DFS or OS between treatment arms for patients who were negative for ctDNA. The rate of ctDNA clearance at week 6 was higher in the atezolizumab arm (18%) than in the observation arm (4%) (p = 0.0204). An ongoing clinical trial (IMvigor011) is evaluating atezolizumab as adjuvant therapy in patients with high-risk MIBC who are ctDNA positive following cystectomy [224]. Although promising, there are currently no validated predictive molecular markers that are routinely used in clinical practice. Further validation studies are awaited.

6.4 Conclusion

The updated TCGA and other efforts have refined our understanding of the molecular underpinnings of BC biology. Molecular subtypes, immune gene signatures as well as stromal signatures may ultimately have an important role in predicting response to IO. Although PD-L1 expression by immunohistochemistry and TMB have demonstrated predictive value in certain settings, additional studies are needed. Prospectively validated prognostic and predictive molecular biomarkers will present valuable adjuncts to clinical and pathological data, but large phase III RCTs with long-term follow-up will be needed to clarify the many questions remaining.

6.5 *Summary of evidence for urothelial markers*

Summary of evidence	LE
There is insufficient evidence to use TMB, molecular subtypes, immune or other gene expression signatures for the management of patients with urothelial cancer.	-

7. DISEASE MANAGEMENT

7.1 Neoadjuvant therapy

7.1.1 Introduction

The standard treatment for patients with urothelial MIBC and MIBC with variant histologies is RC. However, RC only provides 5-year survival in about 50% of patients [225-229]. To improve these results in patients with cN0M0 disease, cisplatin-based NAC has been used since the 1980s [225-231].

7.1.2 Role of cisplatin-based chemotherapy

There are theoretical advantages and disadvantages of administering chemotherapy before planned definitive surgery to patients with resectable muscle-invasive cN0M0 UC of the bladder:

- Chemotherapy is delivered at the earliest time-point, when the burden of micrometastatic disease is expected to be low.
- Potential reflection of *in-vivo* chemosensitivity.
- Tolerability of chemotherapy and patient compliance are expected to be better pre-cystectomy.
- Patients may respond to NAC and have a favourable pathological response as determined mainly by achieving ypT0, ≤ ypT1, ypN0 and negative surgical margins.
- Delayed cystectomy might compromise the outcome in patients not sensitive to chemotherapy [232-234]. A comparative survival analysis of patients treated with NAC and RC vs. RC alone based on data from the National Cancer Database showed that organ-confined disease (≤ pT2) after NAC was associated with decreased risk of death (HR: 0.85, 95% CI: 0.79–0.91) compared to RC alone, whereas > pT2 was associated with increased risk of death (HR: 1.46, 95% CI: 1.34–1.60) [235]. However, there are

no prospective trials indicating that delayed surgery due to NAC has a negative impact on survival. In the phase III VESPER trial, comparing gemcitabine/cisplatin (GC) vs. high-dose-intensity methotrexate, vinblastine, doxorubicine and cisplatin (HD-MVAC) in the peri-operative setting, approximately 90% of patients proceeded to surgery (with median delay of 48 days for GC and 51 days for ddMVAC) [236].

- Neoadjuvant chemotherapy does not seem to affect the outcome of surgical morbidity. In one randomised trial the same distribution of grade 3–4 post-operative complications was seen in both treatment arms [237]. In the combined Nordic trials (n = 620), NAC did not have a major adverse effect on the percentage of performable cystectomies. The cystectomy frequency was 86% in the experimental arm and 87% in the control arm with 71% of patients receiving all three chemotherapy cycles [238].
- Clinical staging using bimanual palpation, CT or MRI may result in over- and understaging and have a staging accuracy of only 70% [78]. Overtreatment is a possible negative consequence.
- Gender may have an impact on chemotherapeutic response and oncologic outcomes [239, 240].
- Neoadjuvant chemotherapy should only be used in patients eligible for cisplatin-combination
- chemotherapy; other combinations (or monotherapies) are inferior in metastatic BC and have not been fully tested in a neoadjuvant setting [237, 241-249].

7.1.2.1 Summary of available data

Several phase III RCTs addressed the potential survival benefit of NAC administration [237, 241-246, 250-254]. The main differences in trial designs were the type of chemotherapy (i.e., single-agent cisplatin or combination chemotherapy) and the number of cycles provided. Patients had to be fit for cisplatin. Since these studies differed considerably for patient numbers, patient characteristics (e.g., clinical T-stages included) and the type of definitive treatment offered (cystectomy and/or RT), pooling of results was not possible.

Three meta-analyses were undertaken to establish if NAC prolongs survival [247-249]. In a meta-analysis including updated patient data from 11 randomised trials (n = 3,005), a significant survival benefit was shown in favour of NAC [249]. The most recent meta-analysis included four additional randomised trials, and used the updated results from the Nordic I, Nordic II, and BA06 30894 trials including data from 427 new patients and updated information from 1,596 patients. The results of this analysis confirmed the previously published data and showed an 8% absolute improvement in survival at five years with a number needed-to-treat of 12.5 [255]. Only cisplatin-combination chemotherapy with at least one additional chemotherapeutic agent resulted in a meaningful therapeutic benefit [247, 249]; the regimens tested were methotrexate, vinblastine, adriamycin (epirubicin) plus cisplatin (MVA(E)C), cisplatin, methotrexate plus vinblastine (CMV), cisplatin plus methotrexate (CM), cisplatin plus adriamycin and cisplatin plus 5-fluorouracil (5-FU) [256].

The updated analysis of a large phase III RCT [241] with a median follow-up of eight years confirmed previous results and provided additional findings:

- 16% reduction in mortality risk;
- improvement in 10-year survival from 30% to 36% with neoadjuvant CMV;
- benefit with regard to distant metastases;
- the addition of neoadjuvant CMV provided no benefit for locoregional control and locoregional DFS, independent of the definitive treatment.

More modern chemotherapeutic regimens such as GC have shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses [256-259]. Modified ddMVAC was tested in two small single-arm phase II studies demonstrating high rates of pathologic complete remission [260, 261]. Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for ddMVAC [262].

The recently reported results from the GETUG/AFU V05 VESPER RCT of perioperative chemotherapy with 6 cycles of ddMVAC vs. 4 cycles of GC in 493 patients (437 neoadjuvant and 56 adjuvant) demonstrated similar pathologic response rates (ypT0N0) in patients treated with ddMVAC 42% and GC 36% (p = 0.2). The < ypT2N0 rate was 63% and 50% in the ddMVAC and GC patients, respectively. Progression-free survival was significantly improved in the NAC receiving ddMVAC as compared to GC (HR = 0.70, 95% CI: 0.51–0.96; p = 0.025), however, the PFS endpoint was not significant in the entire perioperative chemotherapy population (HR: 0.77, 95% CI: 0.57–1.02; p = 0.077). Dose-dense MVAC was associated with more severe asthenia and GI side effects than GC [236]. Another dose-dense regimen using GC was reported in two small phase II trials [263, 264]. While pathological response rates (< pT2) in the range of 45%–57% were achieved, one trial had to be closed prematurely due to high rates of severe vascular events [263]. This approach is therefore not recommended outside of clinical trials.

As an alternative to the standard dose of cisplatin-based NAC with 70 mg/m^2 on day 1, split-dose modifications regimens are often used with 35 mg/m^2 on days 1+8 or days 1+2. In a retrospective analysis

the standard schedule was compared to a split-dose schedule in terms of complete and partial pathological response. A lower number of complete and partial response rates was seen in the split-dose group, but these results were not statistically significant [265].

There seem to be differences in the outcomes of patients treated with NAC for primary or secondary MIBC. However, in the absence of prospective data, patients with secondary MIBC should be treated similarly to those presenting with primary MIBC [208].

It is unclear, if patients with non-UC histology will also benefit from NAC. A retrospective analysis demonstrated that patients with neuroendocrine tumours had improved OS and lower rates of non-organ-confined disease when receiving NAC. In case of micropapillary differentiation, sarcomatoid differentiation and adenocarcinoma, lower rates of non-organ confined disease were found, but no statistically significant impact on OS. Patients with squamous cell carcinoma did not benefit from NAC [266]. A 2019 systematic review showed benefit of NAC for patients with micropapillary-, plasmacytoid-, sarcomatoid-, and mixed variants but especially for patients with neuroendocrine tumours [68].

7.1.3 The role of imaging and predictive biomarkers

Data from small imaging studies aiming to identify responders in patients treated with NAC suggest that response after two cycles of treatment is predictive of outcome. Although mpMRI has the advantage of better resolution of the bladder wall tissue planes as compared to CT, it is not ready yet for standard patient care. However, bladder mpMRI may be useful to inform on tumour stage after TURB and response to NAC [107]. So far PET/CT, MRI or DCE-MRI cannot accurately assess treatment response [267-270]. To identify progression during NAC imaging is being used in many centres notwithstanding the lack of supporting evidence.

For responders to NAC, especially in those with a complete response (pT0 N0), treatment has a major positive impact on OS [271, 272]. Therefore, reliable predictive markers to identify patients most likely to benefit from chemotherapy are needed. Molecular tumour profiling might guide the use of NAC in the future but, as yet, this is not applicable in routine practice [273-275] (see Chapter 6 - Markers).

7.1.4 Role of neoadjuvant immunotherapy

Inhibition of PD-1/PD-L1 checkpoint has demonstrated significant benefit in patients with unresectable and metastatic BC in the second-line setting and in platinum-ineligible PD-L1+ patients as first-line treatment using different agents. Checkpoint inhibitors are increasingly tested also in the neoadjuvant setting; either as monotherapy or in combination with chemotherapy or CTLA-4 checkpoint inhibition. Data from two phase II trials have been presented with encouraging results [219, 220]. The results of the phase II trial using the PD-1 inhibitor pembrolizumab reported a complete pathological remission (pT0) in 42% and pathological response (< pT2) in 54% of patients, whereas in the single-arm phase II trial with atezolizumab a pathologic complete response rate of 31% was reported. In a recent study evaluating neoadjuvant GC plus pembrolizumab in MIBC, the primary endpoint was met with 56% of 46 evaluable patients downstaged to < ypT2N0 and 36% achieving ypT0N0 [276]. However, immunotherapy alone, or in combination, is not yet approved in the neoadjuvant setting.

7.1.5 Summary of evidence and guidelines for neoadjuvant therapy

Summary of evidence	LE
Neoadjuvant cisplatin-containing combination chemotherapy improves OS (5–8% at five years).	1a
Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0 or ≤ ypT2.	2a
Currently immunotherapy with checkpoint inhibitors as monotherapy, or in different combinations, is being tested in phase II and III trials. Initial results are promising.	-
There are still no tools available to select patients who have a higher probability of benefitting from NAC. In the future, genetic markers in a personalised medicine setting might facilitate the selection of patients for NAC and differentiate responders from non-responders.	-

Recommendations	Strength rating
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

7.2 Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

7.2.1 ***Post-operative radiotherapy***

Given the high rates of local-regional failure after RC in patients with locally advanced (pT3–4) BC, estimated at ~30%, as well as the high risk of distant failure and poor survival for these patients, there is an interest in adjuvant therapies that address both the risk of local and distant disease. Data on adjuvant RT after RC are limited and further prospective studies are needed, but a more recent phase II trial compared adjuvant sequential chemotherapy and radiation vs. adjuvant chemotherapy alone in 120 patients with locally advanced disease and negative margins after RC (with one or more risk factors: ≥ pT3b, grade 3, or node-positive), in a study population with 53% UC and 47% SCC. Addition of adjuvant RT to chemotherapy alone was associated with a statistically significant improvement in local relapse-free survival (at 2 years 96% vs. 69% favouring the addition of RT). Disease-free survival and OS also favoured the addition of RT, but those differences were not statistically significant and the study was not powered for those endpoints. Late-grade ≥ 3 GI toxicity in the chemoradiation arm was low (7% of patients) [277].

A 2019 systematic review evaluating the efficacy of adjuvant radiation for BC or UTUC found no clear benefit of adjuvant radiation following radical surgery (e.g., cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease [278].

While there are no conclusive data demonstrating improvements in OS it is reasonable to consider adjuvant radiation in patients with pT3/pT4 pN0–2 urothelial BC following RC, although this approach has been evaluated in only a limited number of studies. Radiation fields should encompass areas at risk for harbouring residual microscopic disease based on pathologic findings at surgery and may include cystectomy bed and pelvic LNs. Doses in the range of 45 to 50.4 Gy may be considered. For patients who have not had prior NAC, it may be reasonable to sandwich adjuvant radiation between cycles of adjuvant chemotherapy. The safety and efficacy of concurrent radiosensitising chemotherapy in the adjuvant setting needs further study.

7.2.2 ***Pre-operative radiotherapy***

To date, six RCTs have been published investigating pre-operative RT, although all are from several decades ago. In the largest trial, pre-operative RT at a dose of 45 Gy was used in patients with muscle-invasive tumours resulting in a significant increase in pathological complete response (9% to 34%) in favour of pre-operative RT, which was also a prognostic factor for survival [279]. The OS data were difficult to interpret since chemotherapy was used in a subset of patients only and more than 50% of patients (241/475) did not receive the planned treatment and were excluded from the final analyses. Two smaller studies using a dose of 20 Gy showed only a small survival advantage in ≥ T3 tumours [280, 281]. Two other small trials confirmed downstaging after pre-operative RT [282, 283].

A meta-analysis of five RCTs showed a difference in 5-year survival (OR: 0.71, 95% CI: 0.48–1.06) in favour of pre-operative RT [284]. However, the meta-analysis was potentially biased by data from the largest trial in which patients were not given the planned treatment. When the largest trial was excluded from the analysis, the OR became 0.94 (95% CI: 0.57–1.55), which was not significant.

A more recent RCT, comparing pre-operative vs. post-operative RT and RC (n = 100), showed comparable OS, DFS and complication rates [285]. Approximately half of these patients had UC, while the other half had SCC.

In general, such older data is limited in being able to provide a robust evidence base for modern guideline recommendations.

7.2.3 ***Summary of evidence and guidelines for pre- and post-operative radiotherapy***

Summary of evidence	**LE**
No contemporary data exists to support that pre-operative RT for operable MIBC increases survival.	2a
Pre-operative RT for operable MIBC, using a dose of 45–50 Gy in fractions of 1.8–2 Gy, results in down-staging after 4 to 6 weeks.	2
Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after RC.	3
Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival following cystectomy for locally-advanced bladder cancer (pT3b–4, or node-positive).	2a

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant radiation in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak

7.3 Radical surgery and urinary diversion

*7.3.1 **Removal of the tumour-bearing bladder***

7.3.1.1 Introduction

Radical cystectomy is the standard treatment for localised MIBC in most Western countries [225, 286]. Increased recognition of the central patient role as a healthcare consumer and a greater focus on patients' QoL contributed to an increasing trend of utilising bladder-preserving treatment modalities, such as radio- and/or chemotherapy (see Section 7.5). Performance status and life expectancy influence the choice of primary management as well as the type of urinary diversion with RC being reserved for patients with a longer life expectancy without concomitant disease and a better PS. Frailty, nutritional status and decreased kidney function are conditions significantly related to an increased risk of post-operative adverse events (AEs) [287-289].

7.3.1.2 Radical cystectomy: timing

A 2020 meta-analysis including 19 studies concluded that a delay of > 3 months has a negative effect on OS (HR: 134, 95% CI: 1.18–1.53). Authors highlighted the lack of standardisation how delays were defined in the included studies which prohibited defining a clear cut-off time, although most studies used a cut-off of < 3 months [290]. Overall conclusion was that BC patients scheduled for RC should be treated without delays to maximise survival.

*7.3.2 **Radical cystectomy: indications***

Traditionally, RC was recommended in patients with T2–T4a, N0–Nx, M0 disease [286]. Other indications include BCG-refractory, BCG-relapsing and BCG-unresponsive NMIBC (see EAU Guidelines on Non-muscle-invasive Bladder Cancer [2]), as well as extensive papillary disease that cannot be controlled with TURB and intravesical chemotherapy alone.

Salvage cystectomy is indicated in non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-UC. It is also used as a purely palliative intervention, including for fistula formation, pain and recurrent visible haematuria (see Section 7.4.1 - Palliative cystectomy).

*7.3.3 **Radical cystectomy: technique and extent***

Different approaches have been described to improve voiding and sexual function in patients undergoing RC for BC. No consensus exists regarding which approach preserves function best. Concern remains regarding the impact of 'sparing-techniques' on oncological outcomes.

To determine the effect of sexual function-preserving cystectomy (SPC) on functional and oncological outcomes the Panel undertook two systematic reviews addressing sparing techniques in men and women [291, 292].

7.3.3.1 Radical cystectomy in men

In men, standard RC includes removal of the bladder, prostate, seminal vesicles, distal ureters, and regional LNs.

7.3.3.1.1 Concomitant prostate cancer

Prostate cancer is found in 21–50% of male patients undergoing RC for BC [293-296]. Incidentally discovered clinically significant prostatic adenocarcinoma did not alter survival [295, 296]. Pathological reporting of the specimens should follow the recommendations as presented in the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer [297].

7.3.3.1.2 Sexual-preserving techniques

Four main types have been described:

1. **Prostate sparing cystectomy:** part of or the whole prostate is preserved including seminal vesicles, vas deferens and neurovascular bundles.
2. **Capsule sparing cystectomy:** the capsule or peripheral part of the prostate is preserved with adenoma (including prostatic urethra) removed by TURP or *en bloc* with the bladder. Seminal vesicles, vas deferens and neurovascular bundles are also preserved.

3. **Seminal sparing cystectomy:** seminal vesicles, vas deferens and neurovascular bundles are preserved.
4. **Nerve-sparing cystectomy:** the neurovascular bundles are the only tissue left in place.

Twelve studies recruiting a total of 1,098 patients were identified, including nine comparative studies [298-308] and three single-arm case series [309-311]. In the majority of cases, an open surgical approach was used and the urinary diversion of choice was an orthotopic neobladder. Median follow-up was longer than three years in nine studies, with three studies presenting results with a median follow-up longer than five years.

The majority of the studies included patients who were potent pre-operatively with organ-confined disease without tumour in the bladder neck and/or prostatic urethra. Prostate cancer was ruled out in all of the SPC techniques, except in nerve-sparing cystectomy.

Oncological outcomes did not differ between groups in any of the comparative studies that measured local recurrence, metastatic recurrence, DSS and OS, at a median follow-up of three to five years. Local recurrence after SPC was commonly defined as any UC recurrence below the iliac bifurcation within the pelvic soft tissue and ranged from 1.2–61.1% vs. 16–55% in the control group. Metastatic recurrence ranged from 0–33.3%.

For techniques preserving prostatic tissue (prostate- or capsule-sparing), rates of incidental prostate cancer in the intervention group ranged from 0–15%. In no case was incidental prostate cancer with ISUP grade ≥ 4 reported.

Post-operative potency was significantly better in patients who underwent any type of sexual-preserving technique compared to conventional RC ($p < 0.05$), ranging from 80–90%, 50–100% and 29–78% for prostate-, capsule- or nerve-sparing techniques, respectively. Data did not show superiority of any sexual-preserving technique.

Urinary continence, defined as the use of 'no pads' in the majority of studies, ranged from 88–100% (day-time continence) and from 31–96% (night-time continence) in the prostate-sparing cystectomy patients. No major impact was shown with regard to continence rates for any of the three approaches.

The evidence base suggests that these procedures may yield better sexual outcomes than standard RC without compromising oncological outcomes. However, the overall quality of the evidence was moderate, and hence if a sexual-preserving technique is offered, patients must be carefully selected, counselled and closely monitored.

7.3.3.1.3 Summary of evidence and recommendations for sexual-preserving techniques in men

Summary of evidence	**LE**
The majority of patients motivated to preserve their sexual function will benefit from sexual-preserving techniques.	2a
None of the sexual-preserving techniques (prostate/capsule/seminal/nerve-sparing) have shown to be superior, and no particular technique can be recommended.	3

Recommendations	**Strength rating**
Do not offer sexual-preserving radical cystectomy to men as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong

7.3.3.2 Radical cystectomy in women

In women, standard RC includes removal of the bladder, the entire urethra and adjacent vagina, uterus, distal ureters, and regional LNs [312]. Pelvic floor disorders, sexual and voiding dysfunction in female patients are prevalent after RC [313]. As part of the pre-operative evaluation a gynaecological history should be obtained and patients should be counselled on the potential negative impact of RC on sexual function and/or vaginal prolapse. Most importantly, a history of cervical cancer screening, abnormal vaginal bleeding and a family history of breast and/or ovarian cancer should be recorded, as well as ruling out possible pelvic organ prolapse. Equally important is screening for sexual and urinary function and prolapse post-operatively. Better imaging modalities, increased knowledge of the function of the pelvic structures and improved surgical

techniques have enabled less destructive methods for treating high-risk BC.

Pelvic organ-preserving techniques involve preserving the neurovascular bundle, vagina, uterus, ovaries or variations of any of the stated techniques. From an oncological point of view, concomitant malignancy in gynaecological organs is rare and local recurrences reported after RC are infrequent [314, 315]. In premenopausal women, by preserving ovaries, hormonal homeostasis will be preserved, decreasing risk of cognitive impairment, cardiovascular diseases and loss of bone density. In case of an increased risk of hereditary breast or ovarian cancer (i.e., *BRCA1/2* mutation carriers or patients with Lynch syndrome), salpingooophorectomy should be advised after childbearing and to all women over 40 years of age [316]. On the other hand, preservation of the uterus and vagina will provide the necessary support for the neobladder, thereby reducing the risk of urinary retention. It also helps to avoid post-operative prolapse as removal of the uterus predisposes to an anterior or posterior vaginal prolapse. In case of an already existing prolapse of the uterus, either isolated or combined with a vaginal prolapse, removing the uterus will be beneficial. It is noteworthy that by resecting the vaginal wall, the vagina shortens which could potentially impair sexual satisfaction and function.

Based on retrospective low quality data only, a systematic review evaluating the advantages and disadvantages of sexual-function preserving RC and orthotopic neobladder in female patients concluded that in well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes [292].

Pelvic organ-preserving RC could be considered also in elderly and fragile patients having abdominal diversions. By reducing excision range, it might be beneficial from the point of reduced operating time, estimated blood loss and quicker bowel recovery [317].

7.3.3.2.1 Summary of evidence and recommendations for sexual-preserving techniques in women

Summary of evidence	**LE**
Data regarding pelvic organ-preserving RC for female patients remain immature.	3

Recommendations	**Strength rating**
Do not offer pelvic organ-preserving radical cystectomy to women as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual organ-preserving techniques to women motivated to preserve their sexual function since the majority will benefit.	Weak
Select patients based on: • absence of tumour in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma.	Strong

*7.3.4 **Lymphadenectomy: role and extent***

Controversies in evaluating the clinical significance of lymphadenectomy (LND) are related to two main aspects of nodal dissection: therapeutic procedure and/or staging instrument.

Two important autopsy studies have been performed for RC so far. The first study showed that in 215 patients with MIBC and nodal dissemination, the frequency of metastasis was 92% in regional (perivesical or pelvic), 72% in retroperitoneal, and 35% in abdominal LNs. There was also a significant correlation between nodal metastases and concomitant distant metastases ($p < 0.0001$). Approximately 47% of the patients had both nodal metastases and distant dissemination and only 12% of the patients had nodal dissemination as the sole metastatic manifestation [318].

The second autopsy study focused on the nodal yield when super-extended pelvic LND was performed. Substantial inter-individual differences were found with counts ranging from 10 to 53 nodes [319]. These findings demonstrate the limited utility of node count as a surrogate for extent of dissection.

Regional LNs have been shown to consist of all pelvic LNs below the bifurcation of the aorta [320-324]. Mapping studies also found that skipping lesions at locations above the bifurcation of the aorta without more distally located LN metastases is rare [324, 325].

The optimal extent of LND has not been established to date. Standard LND in BC patients involves removal of nodal tissue cranially up to the common iliac bifurcation, with the ureter being the medial border, and including the internal iliac, presacral, obturator fossa and external iliac nodes [326]. Extended LND includes all LNs in the region of the aortic bifurcation, and presacral and common iliac vessels medial to the crossing ureters. The lateral borders are the genitofemoral nerves, caudally the circumflex iliac vein, the lacunar ligament and the LN

of Cloquet, as well as the area described for standard LND [326-330]. A super-extended LND extends cranially to the level of the inferior mesenteric artery [331, 332].

In order to assess how and if cancer outcome is influenced by the extent of LND in patients with clinical N0M0 MIBC, a systematic review of the literature was undertaken [333]. Out of 1,692 abstracts retrieved and assessed, nineteen studies fulfilled the review criteria [326-330, 332, 334-346]. All five studies comparing LND vs. no LND reported a better oncological outcome for the LND group. Seven out of twelve studies comparing (super)extended with limited or standard LND reported a beneficial outcome for (super)extended LND in at least a subset of patients which is in concordance with the findings of several other meta-analyses [347, 348]. No difference in outcome was reported between extended and super-extended LND in the two high-volume-centre studies identified [332, 344]. The LEA trial, a prospective phase III RCT, including 401 patients with a median follow-up of 43 months reported [349]. Extended LND failed to show a significant advantage (the trial was designed to show an absolute improvement of 15% in 5-year RFS by extended LND) over limited LND in RFS, CSS, and OS. Results from another large RCT on the therapeutic impact of the extent of LND are expected shortly.

It has been suggested that PFS as well as OS might be correlated with the number of LNs removed during surgery. Although there are no data from RCTs on the minimum number of LNs that should be removed, survival rates increase with the number of dissected LNs [350]. In retrospective studies removal of at least ten LNs has been postulated as sufficient for evaluation of LN status, as well as being beneficial for OS [351]. Submitting separate nodal packets instead of *en bloc* has shown significant increased total LN yield, but did not result in an increased number of positive LNs, making LN density an inaccurate prognosticator [352]. In conclusion, extended LND might have a therapeutic benefit compared to less extensive LND, but due to study bias no firm conclusions can be drawn [333, 353].

7.3.5 ***Laparoscopic/robotic-assisted laparoscopic cystectomy***

A number of recent systematic reviews comparing open RC (ORC) and robot-assisted RC (RARC) reach similar conclusions; RARC has an approximately one-day shorter length of hospital stay (LOS) and less blood loss, but a longer operative time. Complication rates seem similar for both approaches but all published reviews suffer from low quality data.

In minimally-invasive cystectomy, with increasing age, LOS is markedly shorter; up to 2.56 days in patients over 80 years old [354].

Although the low level of evidence of the studies included in these reviews remains a major limitation, a recent Cochrane review incorporating data from all five published RCTs corroborates most findings [355]. Time to recurrence, positive surgical margin rates, grade 3–5 complications and QoL were comparable for RARC and ORC, whilst transfusion rate was likely lower after RARC. For other endpoints outcomes were uncertain due to study limitations.

The Pasadena Consensus Panel (a group of experts on RC, LND and urinary reconstruction) reached similar conclusions [356]. Additionally, they reported that RARC was associated with increased costs, although compared to laparoscopic RC (LRC) there are ergonomic advantages for the surgeon. For both techniques, surgeons' experience and institutional volume strongly predicted outcome. According to the literature, proficiency is reached after 20–250 cases. However, after statistical modelling, the Pasadena Consensus Panel suggested 30 cases but they also concluded that challenging patients (high BMI, post chemotherapy or RT, pelvic surgery, T4 or bulky tumours or positive nodes) should be performed by experienced robotic surgeons only. Safety of RC after RT was confirmed by a small retrospective study (n = 46) [357]. In experienced hands the percentage of 90-day (major) complications after robotic cystectomy was independent of previous RT [358].

Data on post-RC uretero-enteric stricture rates for both ORC and RARC remain inconclusive. Results are mainly reported by high-volume centres or derive from population-based studies with a large variety of endpoints and poor controlling of potential confounders, making comparison difficult [358-363]. From a surgical technique perspective, the main risk-factor for complications comparing ORC and RARC may be tissue handling; the same applies to different diversion techniques in RARC patients, as those managed by extracorporeal diversion (RARC-ECUD) tend to have more strictures compared to intracorporeal diversion (RARC-ICUD) [362]. This is explained by the need for more extensive dissection of ureter in RARC-ECUD, more tension, resulting in impaired blood supply [364, 365].

Positive surgical margins, as a surrogate for oncological outcome, are comparable between RARC and ORC, although with low certainty [355]. Recurrence-free survival, CSS and OS have been documented as similar

in all RCTs including the largest RAZOR (Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer) trial (n = 302) [366]. Age over 70, poor PS and major complications were significant predictors of 36-month PFS whilst stage and positive margins were significant predictors of recurrence, PFS and OS. The surgical approach was not a significant predictor of any outcome. A larger (n = 595) single-centre study with a median follow-up of over five years also found comparable recurrence and survival data, including atypical recurrences (defined as one or a combination of the following: port-site metastasis or peritoneal carcinomatosis) [367]. However, recently, port-site metastases and atypical recurrences were reviewed by Mantica *et al.* [368]. Based on 31 studies and 6,720 evaluable patients, 105 patients (1.63%) were identified with an atypical recurrence, of which 63 (60%) were peritoneal carcinomatosis and 11 (10.5%) port-site metastases. The authors acknowledge, however, that these results may be linked to publication bias and retrospective study design of the included studies. Wei *et al.*, detected residual cancer cells in pelvic washing specimens during or after, but not before, RARC in approximately half of the patients (9/17), which was associated with aggressive variant histology and cancer recurrence. These findings need confirmation in larger studies [369].

The largest RCT to date, the RAZOR trial, supports all of the above findings showing RARC to be non-inferior to ORC in terms of 2-year PFS (72.3% vs. 71.6%), AEs (67% vs. 69%) and QoL [370]. A systematic review of five RCTs including the RAZOR trial supports all of the above findings showing RARC to be non-inferior to ORC with regard to time to recurrence, rates of major complications, QoL, and positive surgical margin rates (all low-certainty evidence) [371].

Most reviewed series, including the RAZOR trial, offer extracorporeal reconstruction. Hussein *et al.*, retrospectively compared extracorporeal reconstruction (n = 1,031) to intracorporeal reconstruction (n = 1,094); the latter was associated with a shorter operative time and fewer blood transfusions but more high-grade complications, which, again, decreased over time [372]. A retrospective report from a high-volume centre found less (major) complications after intracorporeal reconstruction (n = 301) as compared to extracorporeal reconstruction (n = 375) and open RC (n = 272) [373]. It is important to note that, although an intracorporeal neobladder is a very complex robotic procedure [374], the choice for neobladder or cutaneous diversion should not depend on the surgical approach.

An interim analysis of a small RCT of ORC (n = 27) vs. RARC with intracorporeal urinary diversion (n = 24), found comparable results at one year after surgery for most health-related quality of life (HRQoL) domains. Patients receiving ORC were more likely to experience a decline in role functioning and higher symptoms scale, while RARC-intracorporeal urinary diversion patients were more likely to report significant increases in urinary symptoms and problems [375]. A prospective, non-randomised, multicentre comparative effectiveness study showed no statistically significant differences after 12-months between ORC (n = 154) and RARC (n = 159) in terms of complications (67 vs. 64%) and HRQoL [376].

7.3.5.1 Laparoscopic radical cystectomy versus robot-assisted radical cystectomy

For LRC a review including sixteen studies came to similar conclusions as described for RARC [374]. As compared to ORC, LRC had a significantly longer operative time, fewer overall complications, less blood transfusions and analgesic use, less blood loss and a shorter LOS. However, the review was limited by the inherent limitations of the included studies. Although this review also showed better oncological outcomes, these appeared comparable to ORC series in a large LRC multicentre study [377].

The CORAL study was a small single-centre RCT comparing open (n = 20) vs. robotic (n = 20) vs. laparoscopic (n = 19) RC [378, 379]. The 30-day complication rate was significantly higher in the open arm (70%) compared to the laparoscopic arm (26%). There was no difference between the 90-day Clavien complication rates in the three study arms. Limitations of this study include the small sample size, three different although experienced surgeons, and cross over between arms.

7.3.5.2 Summary of evidence and guidelines for laparoscopic/robotic-assisted laparoscopic cystectomy

Summary of evidence	**LE**
Robot-assisted RC has longer operative time (1–1.5 hours) and major costs, but shorter length of hospital stay (1–1.5 days) and less blood loss compared to ORC.	1
Robotic cystectomy and open cystectomy may result in similar rates of (major) complications.	2
Most endpoints, if reported, including intermediate-term oncological endpoint and QoL, are not different between RARC and ORC.	2
Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.	2

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong

*7.3.6 **Urinary diversion after radical cystectomy***

From an anatomical standpoint, three alternatives are currently used after cystectomy:

- abdominal diversion, such as an uretero-cutaneostomy, ileal or colonic conduit, and various forms of a continent pouch (infrequently used);
- urethral diversion, which includes various forms of GI pouches attached to the urethra as a continent orthotopic urinary diversion (neobladder, orthotopic bladder substitution);
- rectosigmoid diversions, such as uretero-(ileo-)rectostomy (infrequently used).

Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix [380].

Several studies have compared certain aspects of HRQoL such as sexual function, urinary continence and body image in patient cohorts with different types of urinary diversion [381]. However, further research evaluating the impact of pre-operative tumour stage, functional- and socio-economic status, and time interval to primary surgery are needed.

7.3.6.1 Patient selection and preparations for surgery

In consultation with the patient, both an orthotopic neobladder and ileal conduit should be considered in case reconstructive surgery exposes the patient to excessive risk (as determined by comorbidity and age).

Ensuring that patients make a well-informed decision about the type of urinary diversion is associated with less decision regret post-operatively, independent of the method selected [382].

Diagnosis of an invasive urethral tumour prior to cystectomy leads to urethrectomy which could be a contraindication for a neobladder reconstruction. If indicated; in males, in case of CIS and extension of tumour in the prostatic urethra, urethral frozen section has to be performed on the cystoprostatectomy specimen just under the verumontanum and on the inferior limits of the bladder neck; in females a urethral frozen section has to be taken just below the bladder neck.

Non-muscle-invasive BC in prostatic urethra or bladder neck biopsies does not necessarily preclude orthotopic neobladder substitution, provided that patients undergo regular follow-up cystoscopy and urinary cytology [383].

In the presence of positive LNs, orthotopic neobladder can nevertheless be considered in case of N1 involvement (metastasis in a single node in the true pelvis) but not in N2 or N3 tumours [384].

Oncological results after orthotopic neobladder substitution or conduit diversion are similar in terms of local or distant metastasis recurrence, but secondary urethral tumours seem less common in patients with a neobladder compared to those with conduits or continent cutaneous diversions [385].

For cystectomy, general preparations are necessary as for any other major pelvic and abdominal surgery. If the urinary diversion is constructed from GI segments, the length or size of the respective segments and their pathophysiology when storing urine must be considered [386]. Despite the necessary interruption and re-anastomosis of the bowel, formal bowel preparation may not be necessary [387]. Bowel recovery time can be reduced by the use of early mobilisation and early oralisation, GI stimulation with metoclopramide and chewing gum [388]. Patients treated according to the 'Fast tract'/ERAS (Early Recovery After Surgery) protocol have shown to score better on the emotional and physical functioning scores and suffer less from wound healing disorders, fever and thrombosis [389].

A cornerstone of the ERAS protocol is post-operative pain management, which involves significantly reducing the use of opioids; offering opioids mainly as breakthrough pain medication. Instead of patient-controlled analgesia and epidural opioids, most patients receive high-dose acetaminophen and/or ketorolac, starting intra-operatively. Patients on ERAS experience more pain as compared to patients on a traditional protocol (Visual Analogue Scale 3.1 vs. 1.1, $p < 0.001$), but post-operative ileus decreased from 22% to 7.3% ($p = 0.003$) [390].

A multicentre randomised placebo-controlled trial showed that patients receiving alvimopan, a peripherally acting μ-opioid receptor antagonist, had quicker bowel recovery compared to patients receiving placebo [391]. However, this drug is, as yet, not approved in Europe.

Venous thromboembolism (VTE) prophylaxis may be implemented as part of an ERAS protocol. A single-centre non-randomised study showed a significant lower 30-day VTE incidence rate in patients treated for 28 days with enoxaparin compared to patients without prophylaxis [392]. Data from the Ontario Cancer

Registry including 4,205 cystectomy patients of whom 1,084 received NAC showed that VTE rates are higher in patients treated with NAC as compared to patients treated with cystectomy only (12% vs. 8%, p = 0.002) [393, 394].

Patients undergoing continent urinary diversion must be motivated to learn about their diversion and to be manually skilful in manipulating their diversion. Contraindications to more complex forms of urinary diversion include:

- debilitating neurological and psychiatric illnesses;
- limited life expectancy;
- severe impaired liver or renal function;
- urothelial carcinoma positive surgical margins.

Relative contraindications specific for an orthotopic neobladder are high-dose pre-operative RT, complex urethral stricture disease and severe urethral sphincter-related incontinence [395].

7.3.6.2 Different types of urinary diversion

Radical cystectomy and urinary diversion are the two steps of one operation. However, the literature uniformly reports complications of RC while ignoring the fact that most complications are diversion related [396]. Age alone is not a criterion for offering continent diversion [395, 397]. Comorbidity, cardiac- and pulmonary function and cognitive function are all important factors that should be considered, along with the patient's social support and preference.

Age > 80 years is often considered to be the threshold after which neobladder reconstruction is not recommended. However, there is no exact age for a strict contraindication. In most large series from experienced centres, the rate of orthotopic bladder substitution after cystectomy for bladder tumour is up to 80% in men and 50% in women [398-401]. Nevertheless, no RCTs comparing conduit diversion with neobladder or continent cutaneous diversion have been performed.

A retrospective study including 1,383 patients showed that the risk of a decline in estimated glomerular filtration rate (eGFR) did not significantly differ after ileal conduit vs. neobladder in patients with pre-operative chronic kidney disease 2 (eGFR 60–89 mL/min/1.73 m^2) or 3a (eGFR 45–59 mL/min/1.73 m^2) [402]. Only age and anastomotic strictures were found to be associated with a decline in eGFR.

7.3.6.2.1 Uretero-cutaneostomy

Ureteral diversion to the abdominal wall is the simplest form of cutaneous diversion. Operating time, complication rate, blood loss, transfusion rate, stay at intensive care and length of hospital stay are lower in patients treated with ureterocutaneostomy as compared to ileal conduit [403, 404]. Therefore, in frail patients and/or in those with a solitary kidney who need a supravesical diversion, uretero-cutaneostomy is the preferred procedure [405, 406]. Quality of life, which was assessed using the Bladder Cancer Index (BCI), showed equal urinary bother and function for patients treated with ileal conduit and uretero-cutaneostomy [403]. However, maintaining a catheter for stoma patency might relate to an elevated incidence of urinary tract infections and therefore impair QoL [407, 408]. Nevertheless, in carefully selected elderly patients, all other forms of wet and dry urinary diversions, including orthotopic bladder substitutions, are possible [409].

Technically, in case patients have both kidneys; either one ureter, to which the other shorter one is attached end-to-side, is connected to the skin (trans-uretero-cutaneostomy) or both ureters are directly anastomosed to the abdominal wall creating a stoma. Due to the smaller diameter of the ureters, stoma stenosis has been observed more frequently for this technique as compared to using small or large bowel to create an intestinal stoma [405].

In a retrospective multicentre study peri-operative morbidity was evaluated for urinary diversion using bowel as compared to uretero-cutaneostomy. Patients selected for a uretero-cutaneostomy were older and had a higher ASA score, while their mean Charlson score was lower (4.2 vs. 5.6, p < 0.001) [410].

Despite the limited comparative data available, it must be taken into consideration that older data and clinical experience suggest ureter stenosis at the skin level and ascending UTI are more frequent complications in uretero-cutaneostomy compared to an ileal conduit diversion. In a retrospective study comparing various forms of intestinal diversion, ileal conduits had fewer late complications than continent abdominal pouches or orthotopic neobladders [411].

7.3.6.2.2 Ileal conduit

The ileal conduit is an established option with well-known/predictable results. However, up to 48% of patients develop early complications including UTIs, pyelonephritis, ureteroileal leakage and stenosis [411]. The main complications in long-term follow-up studies are stomal complications in up to 24% of patients and functional

and/or morphological changes of the UUT in up to 30% [411-413]. An increase in complications was seen with longer follow-up in the Berne series of 131 patients who were followed for a minimum of five years (median follow-up 98 months) [414]; the rate of complications increased from 45% at five years to 94% in those surviving > 15 years. In the latter group, 50% of patients developed UUT changes and 38% developed urolithiasis.

7.3.6.2.3 Orthotopic neobladder

According to Dutch-, German- and Spanish bladder cancer registry data, an orthotopic bladder substitution to the urethra is used in approximately 10–20% of both male and female patients. Contemporary reports document the safety and long-term reliability of this procedure. In several large centres, this has become the diversion of choice for most patients undergoing cystectomy [226, 286, 395]. However, in elderly patients (> 80 years) it is rarely performed even in high-volume expert centres [415, 416].

The terminal ileum is the GI segment most often used for bladder substitution. There is less experience with the ascending colon, including the caecum, and the sigmoid [286]. Emptying of the reservoir anastomosed to the urethra requires abdominal straining, intestinal peristalsis, and sphincter relaxation. Early and late morbidity in up to 22% of patients is reported [417, 418]. In two studies of 1,054 and 1,300 patients [395, 419], long-term complications included diurnal (8–10%) and nocturnal (20–30%) incontinence, uretero-intestinal stenosis (3–18%), metabolic disorders, and vitamin B12 deficiency. A study comparing cancer control and patterns of disease recurrence in patients with neobladder and ileal conduit showed no difference in CSS between the two groups when adjusting for pathological stage [420]. Urethral recurrence in neobladder patients seems rare (1.5–7% in both male and female patients) [395, 421]. These results indicate that neobladder in male and female patients does not compromise the oncological outcome of cystectomy. It remains debatable whether patient's QoL for neobladder is better compared to non-continent urinary diversion [422, 423].

Continent cutaneous urinary diversion (a low-pressure detubularised ileal reservoir for self-catheterisation) and uretero-rectosigmoidostomy are rarely used techniques nowadays, due to their high complication rates, including stomal stenosis, incontinence in the continent cutaneous diversion, UUT infections and stone formation in case of uretero-rectosigmoidostomy [424].

Various forms of UUT reflux protection, including a simple isoperistaltic tunnel, ileal intussusception, tapered ileal prolongation implanted subserosally, and direct (sub)mucosal or subserosal ureteral implantation, have been described [418, 425]. According to the long-term results, the UUT is protected sufficiently by either method.

A detailed investigation of the bladder neck prior to RC is important for women who are scheduled for an orthotopic bladder substitute [426]. In women undergoing RC the rate of concomitant urethral malignancy has been reported to range from 12–16% [427]. Localisation of the primary tumour at the bladder neck correlated strongly with concomitant urethral malignancy. In addition, tumour involving the bladder neck and urethra tended to be associated with a higher risk of advanced stage and nodal involvement [428].

Currently, it is not possible to recommend a particular type of urinary diversion. However, most institutions prefer ileal orthotopic neobladders and ileal conduits based on clinical experience [429, 430]. In selected patients, such as patients with a single kidney, uretero-cutaneostomy is surgically the least burdensome type of diversion. Recommendations related to RC and urinary diversions are listed in Section 7.3.10.

*7.3.7 **Morbidity and mortality***

In three long-term studies and one population-based cohort study, the peri-operative mortality was reported as 1.2–3.2% at 30 days and 2.3–8.0% at 90 days [226, 396, 398, 431, 432]. In a large single-centre series early complications (within three months of surgery) were seen in 58% of patients [396]. Late morbidity was usually linked to the type of urinary diversion (see also above) [399, 433]. Early morbidity associated with RC for NMIBC (at high risk for disease progression) is similar and no less than that associated with muscle-invasive tumours [434]. In general, lower morbidity and (peri-operative) mortality have been observed by surgeons and in hospitals with a higher case load and therefore more experience [431, 435-439].

Table 7.1: Management of neobladder morbidity (30-64%) [440]

CLAVIEN System		Morbidity	Management
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.	**Immediate complications:**	
		Post-operative ileus	Nasogastric intubation (usually removed at day 1) Chewing gum Avoid fluid excess and hypovolemia (provoke splanchnic hypoperfusion)
		Post-operative nausea and vomiting	Antiemetic agent (decrease opioids) Nasogastric intubation
		Urinary infection	Antibiotics, no ureteral catheter removal Check the 3 drainages (ureters and neobladdder)
		Ureteral catheter obstruction	Inject 5 cc saline in the ureteral catheter to resolve the obstruction Increase volume infusion to increase diuresis
		Intra-abdominal urine leakage (anastomosis leakage)	Check drainages and watchful waiting
		Anaemia well tolerated	Martial treatment (give iron supplement)
		Late complications:	
		Non compressive lymphocele	Watchful waiting
		Mucus cork	Cough Indwelling catheter to remove the obstruction
		Incontinence	Urine analysis (infection), echography (post-void residual) Physiotherapy
		Retention	Drainage and self-catheterisation education
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Anaemia badly tolerated or if myocardial cardiopathy history	Transfusion[1,2]
		Pulmonary embolism	Heparinotherapy[3]
		Pyelonephritis	Antibiotics and check kidney drainage (nephrostomy if necessary)
		Confusion or neurological disorder	Neuroleptics and avoid opioids
Grade III	Requiring surgical, endoscopic or radiological intervention	Ureteral catheter accidentally dislodged	Indwelling leader to raise the ureteral catheter
		Anastomosis stenosis (7%)	Renal drainage (ureteral catheter or nephrostomy)
		Ureteral reflux	No treatment if asymptomatic
III-a	Intervention not under general anaesthesia	Compressive lymphocele	Transcutaneous drainage or intra-operative marsupialisation (cf grade III)
III-b	Intervention under general anaesthesia	Ileal anastomosis leakage	Ileostomy, as soon as possible
		Evisceration	Surgery in emergency
		Compressive lymphocele	Surgery (marsupialisation)

Grade IV	Life-threatening complication (including central nervous system complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring intensive care/ intensive care unit management.	Rectal necrosis	Colostomy
		Neobladder rupture	Nephrostomy and indwelling catheter/surgery for repairing neobladder
		Severe sepsis	Antibiotics and check all the urinary drainages and CT scan in emergency
IV-a	Single organ dysfunction (including dialysis)	Non-obstructive renal failure	Bicarbonate/aetiology treatment
IV-b	Multi-organ dysfunction	Obstructive pyelonephritis and septicaemia	Nephrostomy and antibiotics
Grade V	Death of a patient		
Suffix 'd'	*If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.*		

[1] *A systematic review showed that peri-operative blood transfusion (PBT) in patients who undergo RC correlates with increased overall mortality, CSM and cancer recurrence. The authors hypothesised that this may be caused by the suggested immunosuppressive effect of PBT. The foreign antigens in transfused blood induce immune suppression, which may lead to tumour cell spread, tumour growth and reduced survival in already immunosuppressed cancer patients. As other possible causes for this finding increased post-operative infections and blood incompatibility were mentioned [441]. Buchner and co-workers showed similar results in a retrospective study. The 5-year CSS decreased in cases where intra-operative blood transfusion (CSS decreased from 67% to 48%) or post-operative blood transfusion (CSS decreased from 63% to 48%) were given [442].*

[2] *Intra-operative tranexamin acid infusion reduces peri-operative blood transfusion rates from 57.7% to 31.1%. There was no increase seen in peri-operative VTE [443].*

[3] *Hammond and co-workers reviewed 20,762 cases of VTE after major surgery and found cystectomy patients to have the second highest rate of VTE among all cancers studied [444]. These patients benefit from 30 days low-molecular-weight heparin prophylaxis. Subsequently, it was demonstrated that BMI > 30 and non-urothelial BCs are independently associated with VTE after cystectomy. In these patients extended (90 days) heparin prophylaxis should be considered [445].*

7.3.8 ***Survival***

According to a multi-institutional database of 888 consecutive patients undergoing RC for BC, the 5-year RFS rate was 58% and CSS was 66% [413]. External validation of post-operative nomograms for BC-specific mortality showed similar results, with bladder-CSS of 62% [446].

Recurrence-free survival and OS in a large single-centre study of 1,054 patients was 68% and 66% at five years and 60% and 43%, at ten years, respectively [212]. However, the 5-year RFS in node-positive patients who underwent cystectomy was considerably less at 34–43% [447, 448]. In a surgery-only study, the 5-year RFS was 76% in patients with pT1 tumours, 74% for pT2, 52% for pT3, and 36% for pT4 [225].

A trend analysis based on 148,315 BC patients identified in the SEER database between 1973 and 2009 showed increased stage-specific 5-year survival rates for all stages, except for metastatic disease [449].

7.3.9 ***Impact of hospital and surgeon volume on treatment outcomes***

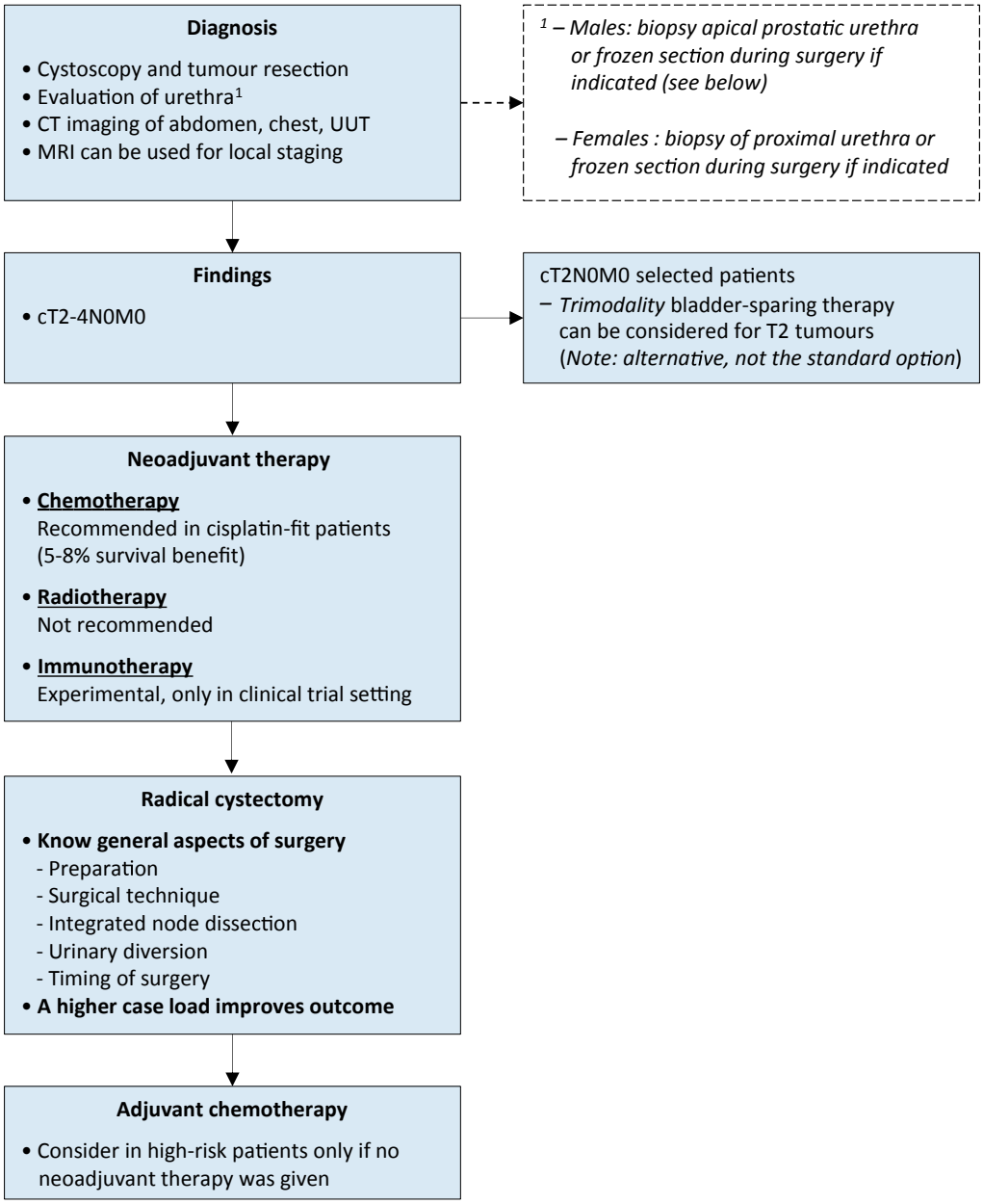
In a systematic review including 40 retrospective studies and 560,00 patients, the impact of hospital and/ or surgeon volume and peri-operative outcomes of RC was assessed [450]. A higher hospital volume was associated with lower in-hospital, 30-day and 90-day mortality. In addition, higher volume hospitals were more likely to have lower positive surgical margins, higher number of LNDs and neobladders and lower complication rates. For surgeon volume, less evidence was available. This study suggested performing at least 10 RCs per centre annually and preferably more than 20. Recently, a nationwide analysis of the Dutch Cancer Registry including almost 9,500 patients between 2008 and 2018 reported decreased 30- and 90-day mortality rates for annual hospital volumes of > 30 RCs. Furthermore, this study showed no true plateau curve for 30- and 90-day mortality beyond 30 RCs supporting the 'more is better' principle [451, 452].

7.3.10 *Summary of evidence and guidelines for radical cystectomy and urinary diversion*

Summary of evidence	LE
Ensuring that patients are well informed about the various urinary diversion options prior to making a decision may help prevent or reduce decision regret, independent of the method of diversion selected.	3
Higher RC hospital volume is associated with lower post-operative mortality rates and higher quality of care.	3
Radical cystectomy includes removal of regional LNs.	3
There are data to support that extended LND (vs. standard or limited LND) improves survival after RC.	3
Radical cystectomy in both sexes must not include removal of the entire urethra in all cases, which may then serve as the outlet for an orthotopic bladder substitution. The terminal ileum and colon are the intestinal segments of choice for urinary diversion.	3
The type of urinary diversion does not affect oncological outcome.	3
The use of extended venous thromboembolism (VTE) prophylaxis significantly decreases the incidence of VTE after RC.	3
In patients aged > 80 years with MIBC, cystectomy is an option.	3
Surgical outcome is influenced by comorbidity, age, previous treatment for bladder cancer or other pelvic diseases, surgeon and hospital volumes of cystectomy, and type of urinary diversion.	2
Surgical complications of cystectomy and urinary diversion should be reported using a uniform grading system. Currently, the best-adapted grading system for cystectomy is the Clavien grading system.	2
No conclusive evidence exists as to the optimal extent of LND.	2a

Recommendations	Strength rating
Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.	Strong
Perform at least 10, and preferably > 20, RCs per hospital/per year.	Strong
Before RC, fully inform the patient about the benefits and potential risks of all possible alternatives. The final decision should be based on a balanced discussion between the patient and the surgeon.	Strong
Do not offer an orthotopic bladder substitute diversion to patients who have a tumour in the urethra or at the level of urethral dissection.	Strong
Pre-operative bowel preparation is not mandatory. ‘Fast track’ measurements may reduce the time to bowel recovery.	Strong
Offer pharmacological prophylaxis, such as low-molecular-weight heparin to RC patients, starting the first day post-surgery, for a period of 4 weeks.	Strong
Offer RC to patients with T2–T4a, N0M0 disease or high-risk non-muscle-invasive bladder cancer.	Strong
Perform a lymph node dissection as an integral part of RC.	Strong
Do not preserve the urethra if margins are positive.	Strong

Figure 7.1: Flow chart for the management of T2–T4a N0M0 urothelial bladder cancer


Diagnosis
• Cystoscopy and tumour resection
• Evaluation of urethra[1]
• CT imaging of abdomen, chest, UUT
• MRI can be used for local staging
[1] – Males: biopsy apical prostatic urethra or frozen section during surgery if indicated (see below)
– Females : biopsy of proximal urethra or frozen section during surgery if indicated
Findings
• cT2-4N0M0
cT2N0M0 selected patients
– Trimodality bladder-sparing therapy can be considered for T2 tumours (Note: alternative, not the standard option)
Neoadjuvant therapy
• Chemotherapy
Recommended in cisplatin-fit patients (5-8% survival benefit)
• Radiotherapy
Not recommended
• Immunotherapy
Experimental, only in clinical trial setting
Radical cystectomy
• Know general aspects of surgery
- Preparation
- Surgical technique
- Integrated node dissection
- Urinary diversion
- Timing of surgery
• A higher case load improves outcome
Adjuvant chemotherapy
• Consider in high-risk patients only if no neoadjuvant therapy was given

CT = computed tomography; MRI = magnetic resonance imaging; UUT = upper urinary tract.

7.4 Unresectable tumours

*7.4.1 **Palliative cystectomy***

Unresectable locally advanced tumours (T4b, invading the pelvic or abdominal wall) may be accompanied by several debilitating symptoms, including bleeding, pain, dysuria and urinary obstruction. These patients are candidates for palliative treatments, such as palliative RT. If control of the symptoms is not possible by less invasive methods, patients may be offered a palliative cystectomy with urinary diversion or urinary diversion only. Palliative cystectomy carries the greatest morbidity, particularly in patients with a poor PS. In a series of 74 patients who underwent palliative cystectomy, severe complications (Clavien-Dindo grade ≥ 3) occurred in 30%. The 30-day mortality rate was 9% and at eight months follow-up, 70% had died [453].

7.4.1.1 Guidelines for unresectable tumours

Recommendations	Strength rating
Offer radical cystectomy as a palliative treatment to patients with locally advanced tumours (T4b).	Weak
Offer palliative cystectomy to patients with symptoms if control is not possible by less invasive methods.	Weak

*7.4.1.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

Consensus statement
In patients with clinical T4 or clinical N+ disease (regional), radical chemoradiation can be offered accepting that this may be palliative rather than curative in outcome.
Chemoradiation should be given to improve local control in cases of inoperable locally advanced tumours.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*

*7.4.2 **Supportive care***

7.4.2.1 Obstruction of the upper urinary tract

Unilateral (best kidney) or bilateral nephrostomy tubes provide the easiest solution for UUT obstruction, but patients find the tubes inconvenient and prefer ureteral stenting. However, stenting can be difficult to achieve. Stents must be regularly replaced and there is the risk of stent obstruction or displacement. Another possible solution is a urinary diversion with, or without, a palliative cystectomy.

7.4.2.2 Bleeding and pain

In the case of bleeding, the patient must be screened first for coagulation disorders or the patient's use of anticoagulant drugs must be reviewed. Transurethral (laser) coagulation may be difficult in a bladder full of tumour or with a bleeding tumour. Intravesical rinsing of the bladder with 1% silver nitrate or 1–2% alum can be effective [454]. This can usually be done without any anaesthesia. The instillation of formalin (2.5–4% for 30 minutes) is a more aggressive and painful procedure, requiring anaesthesia. Formalin instillation has a higher risk of side-effects, e.g., bladder fibrosis, but is more likely to control the bleeding [454]. Vesicoureteral reflux should be excluded to prevent renal complications.

Radiation therapy is another common strategy to control bleeding and is also used to control pain. An older study reported control of haematuria in 59% of patients and pain control in 73% [455]. Irritative bladder and bowel complaints due to irradiation are possible, but are usually mild. Non-conservative options are embolisation of specific arteries in the small pelvis, with success rates as high as 90% [454]. Radical surgery is a last resort and includes cystectomy and diversion (see above, Section 7.4.1).

7.5 Bladder-sparing treatments for localised disease

*7.5.1 **Transurethral resection of bladder tumour***

Transurethral resection of bladder tumour alone in MIBC patients is only possible as a therapeutic option if tumour growth is limited to the superficial muscle layer and if re-staging biopsies are negative for residual (invasive) tumour [456]. In general, approximately 50% of patients will still have to undergo RC for recurrent MIBC with a disease-specific mortality rate of up to 47% in this group [457]. A disease-free status at re-staging TURB appears to be crucial in making the decision not to perform RC [458, 459]. A prospective study by Solsona *et al.*, including 133 patients with radical TURB and re-staging negative biopsies, reported a 15-year follow-up [459]. Thirty per cent of patients had recurrent NMIBC and went on to intravesical therapy, and 30% (n = 40) progressed, of which 27 died of BC. After five, ten, and fifteen years, the results showed CSS rates of 81.9%, 79.5%, and 76.7%, respectively and PFS rates with an intact bladder of 75.5%, 64.9%, and 57.8%, respectively.

In conclusion, TURB alone should only be considered as a therapeutic option for muscle-invasive disease after radical TURB, when the patient is unfit for cystectomy, or refuses open surgery, or as part of a trimodality (TMT) bladder-preserving approach.

7.5.1.1 Guideline for transurethral resection of bladder tumour

Recommendation	Strength rating
Do not offer transurethral resection of bladder tumour alone as a curative treatment option as most patients will not benefit.	Strong

*7.5.2 **External beam radiotherapy***

Current RT techniques with soft-tissue matching and image guidance result in superior bladder coverage and a reduced integral dose to the surrounding tissues. The target total dose (to bladder and/or bladder tumour) for curative EBRT in BC is 64–66 Gy [460, 461]. A reasonable alternative is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions in terms of invasive

locoregional control, OS, and late toxicity. In a phase II study, 55 patients (median age 86) with BC, unfit for cystectomy or even daily RT, were treated with 6-weekly doses of 6 Gy [462]. Forty-eight patients completed EBRT with acceptable toxicity and 17% showed local progression after two years demonstrating good local control with this more ultra-hypofractionated schedule.

Elective treatment to the LNs is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints based on the clinical scenario.

The use of modern standard EBRT techniques results in major related late morbidity of the urinary bladder or bowel in less than 5% of patients [463]. Acute diarrhoea is reduced even more with intensity-modulated RT [464]. Important prognostic factors for outcome include response to EBRT, tumour size, hydronephrosis, presence of CIS, and completeness of the initial TURB. Additional prognostic factors reported are age and stage [465].

With the use of modern EBRT techniques, efficacy and safely results seem to have improved over time. A 2002 Cochrane analysis demonstrated that RC has an OS benefit compared to RT [466], although this was not the case in a 2014 retrospective review using a propensity score analysis [467]. In a 2017 retrospective cohort study of U.S. National Cancer Data Base data, patients over 80 were identified with cT2–4, N0–3, M0 BC, who were treated with curative EBRT (60–70 Gy, n = 739) or concurrent chemoradiotherapy (n = 630) between 2004 and 2013 [468]. The 2-year OS was 42% for EBRT vs. 56% for chemoradiotherapy ($p < 0.001$). For EBRT a higher RT dose and a low stage were associated with improved OS.

In conclusion, although EBRT results seem to improve over time, EBRT alone does not seem to be as effective as surgery or TMT therapy (see Section 7.5.4). Factors that influence outcome should be considered. However, EBRT can be an alternative treatment in patients unfit for radical surgery or concurrent chemotherapy, and it can also be quite effective in helping control bleeding.

7.5.2.1 Summary of evidence and guideline for external beam radiotherapy

Summary of evidence	LE
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy.	3
Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.	3

Recommendation	Strength rating
Do not offer radiotherapy alone as primary therapy for localised bladder cancer.	Strong

*7.5.2.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

Consensus statement
Radiotherapy alone (single block) is not the preferred radiotherapeutic schedule.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy.

*7.5.3 **Chemotherapy***

Chemotherapy alone rarely produces durable complete remissions. In general, a clinical complete response rate of up to 56% is reported in some series, which must be weighed against a staging error of > 60% [469, 470]. Response to chemotherapy is a prognostic factor for treatment outcome and eventual survival although it may be confounded by patient selection [471].

Several groups have reported the effect of chemotherapy on resectable tumours (neoadjuvant approach), as well as unresectable primary tumours [237, 254, 472, 473]. Neoadjuvant chemotherapy with two to three cycles

of MVAC or CMV has led to a down-staging of the primary tumour in various prospective series [237, 254, 472].

A bladder-conserving strategy with TURB and systemic cisplatin-based chemotherapy has been reported several years ago and could lead to long-term survival with intact bladder in a highly selected patient population [471].

A recent large retrospective analysis of a National Cancer Database cohort reported on 1,538 patients treated with TURB and multi-agent chemotherapy [474]. The two and 5-year OS for all patients was 49% and 32.9% and for cT2 patients it was 52.6% and 36.2%, respectively. While these data show that long-term survival with intact bladder can be achieved in a subset of patients it is not recommended for routine use.

7.5.3.1 Summary of evidence and guideline for chemotherapy

Summary of evidence	LE
Complete and partial local responses have been reported with cisplatin-based chemotherapy as primary therapy for locally advanced tumours in highly selected patients.	2b

Recommendation	Strength rating
Do not offer chemotherapy alone as primary therapy for localised bladder cancer.	Strong

*7.5.4 **Trimodality bladder-preserving treatment***

Trimodality therapy combines TURB, chemotherapy and RT. The rationale to combine TURB with RT is to maximally achieve local tumour control in the bladder and adjacent nodes. The addition of radiosensitising chemotherapy or other radiosensitisers (mentioned below) is aimed at the potentiation of RT. Micrometastases are targeted by platinum-based combination chemotherapy (for details see Section 7.1). The aim of TMT is to preserve the bladder and QoL without compromising oncological outcome.

There are no successfully completed RCTs comparing the outcome of TMT with RC, but TMT using chemoradiation has been shown to be superior to RT alone [475-477]. Many of the reported series have differing characteristics as compared to the larger surgical series, which typically have median ages in the mid-to-late 60s compared to mid-70s for some large RT series (reviewed by James, *et al.* [475]). Data from a retrospective series, with some methodological caveats, comparing RT (n = 66) and chemoradiation (n = 208) showed an improved complete response of chemoradiation vs. RT (OR: 2.32; 95% CI: 1.05–5.12; p = 0.037), with a 64% 5-year OS for chemoradiation vs. 45% for RT (HR: 0.7; 95% CI: 0.50–0.99; p = 0.045) [477].

In the case of TMT, two distinct patterns of care emerge; treatment aimed at patients fit for cystectomy who elect TMT or refuse cystectomy, and treatment aimed at older, less fit, patients. For the former category, TMT presents selective bladder preservation and in this case the initial step is a radical TURB where as much tumour as possible should be resected. In this case appropriate patient selection (e.g., T2 tumours, no CIS) is critical [478, 479]. Even in case of an initial presumed complete resection, a second TUR has been suggested to reveal tumour in > 50% of patients and subsequently improves 5-year OS in case of TMT [480]. For patients who are not candidates for cystectomy, less stringent criteria can be applied, but extensive CIS and poor bladder function should both be regarded as relative contraindications.

A collaborative review has described the principles of TMT [481]. For radiation, two schedules are most commonly used; historically within the RTOG a split-course format with interval cystoscopy [476] and single-phase treatment which is now more commonly used [475]. A conventional radiation schedule includes EBRT to the bladder and limited pelvic LNs with an initial dose of 40-45 Gy, with a boost to the whole bladder of 50–54 Gy and a further tumour boost to a total dose of 60–66 Gy. If not boosting the tumour, it is also reasonable for the whole bladder to be treated to 59.4–66 Gy. For node-positive disease, consider boosting grossly involved nodes to the highest achievable dose that does not violate normal tissue constraints. Therefore, elective treatment to the LNs (when node negative) is optional and should take into account patient comorbidities and the risks of toxicity to adjacent critical structures.

In summary, reasonable radiation fields include pelvis (with bladder and/or bladder tumour boost), bladder only or partial bladder (tumour) only [475]. A reasonable radiation dosing alternative to conventional fractionation when treating the bladder-only fields is moderately hypofractionated EBRT to 55 Gy in 20 fractions which has been suggested to be non-inferior to 64 Gy in 32 fractions (fx) in terms of invasive loco-regional control, OS and late toxicity [460, 482].

Different chemotherapy regimens have been used, but most evidence exists for cisplatin [483] and mitomycin C plus 5-FU [475]. In addition to these agents, other regimens have also been used such as gemcitabine and hypoxic cell sensitisation with nicotinamide and carbogen, without clear preference for a specific radiosensitiser [8, 9]. In a recently published phase II RCT, twice-a-day radiation plus fluorouracil/cisplatin was compared to once-daily radiation plus gemcitabine [484]. Both arms were found to result in a > 75% freedom of distant metastases at 3 years (78% and 84%, respectively). Therefore, there are options for non-cisplatin candidates such as 5-FU/mitomycin C or low-dose gemcitabine.

To detect non-responders who should be offered salvage cystectomy, bladder biopsies should be performed after TMT [477].

Five-year CSS and OS rates vary between 50%–84% and 36%–74%, respectively, with salvage cystectomy rates of 10–30% [475, 478, 481, 483, 485, 486]. The Boston group reported on their experience in 66 patients with mixed variant histologies treated with TMT and found similar complete response, OS, DSS and salvage cystectomy rates as in UC [487]. The majority of recurrences post-TMT are non-invasive and can be managed conservatively [475]. In contemporary experiences, salvage cystectomy is required in about 10–15% of patients treated with TMT and can be curative [475, 478, 486]. Current data suggest that major late complication rates are slightly higher but remain acceptable for salvage- vs. primary cystectomy [488, 489].

A sub-analysis of two RTOG trials looked at complete response (T0) and near-complete response (Ta or Tis) after TMT [490]. After a median follow-up of 5.9 years 41/119 (35%) of patients experienced a bladder recurrence, and fourteen required salvage cystectomy. There was no difference between complete and near-complete responders. Non-muscle-invasive BC recurrences after complete response to TMT were reported in 25% of patients by the Boston group, sometimes over a decade after initial treatment [491]. A NMIBC recurrence was associated with a lower DSS, although in properly selected patients, intravesical BCG could avoid immediate salvage cystectomy.

The differential impact of RC vs. TMT on long-term OS is lacking a randomised comparison and rigorous prospective data. A propensity score matched institutional analysis has suggested similar DSS and OS between TMT and RC [486]. Two retrospective analyses of the National Cancer Database from 2004–2013 with propensity score matching compared RC to TMT. Ritch *et al.*, identified 6,606 RC and 1,773 TMT patients [492]. Worse survival was linked to higher age, comorbidity and tumour stage. After modelling, TMT resulted in a lower mortality at one year (HR: 0.84, 95% CI: 0.74–0.96, p = 0.01). However, in years 2 and onwards, there was a significant and persistent higher mortality after TMT (year 2: HR: 1.4, 95% CI: 1.2–1.6, p < 0.001; and year 3 onwards: HR: 1.5, 95% CI: 1.2–1.8, p < 0.001). The second analysis was based on a larger cohort, with 22,680 patients undergoing RC; 2,540 patients received definitive EBRT and 1,489 TMT [493]. Survival after modelling was significantly better for RC compared to any EBRT, definitive EBRT and TMT (HR: 1.4, 95% CI: 1.2–1.6) at any time point. In older patients which are potentially less ideal candidates for radical surgery, Williams *et al.*, found a significantly lower OS (HR :1.49, 1.31–1.69) and CSS (1.55, 1.32–1.83) for TMT as compared to surgery as well as increased costs [494]. This was a retrospective SEER database study which included 687 propensity-matched patients in each arm, however, the median number of radiation fractions was well below what is considered adequate for definitive therapy and as such the radiation patients may have been treated inadequately or palliatively. In general, such population-based studies are limited by confounding, misclassification, and selection bias. A systematic review including 57 studies and over 30,000 patients comparing RC and TMT found improved 10-year OS and DSS for TMT, but for the entire cohort OS and DSS did not significantly differ between RC and TMT [495]. Complete response after TMT resulted in significantly better survival, as did down-staging after TURB or NAC in case of RC.

Overall significant late pelvic (GI/genitourinary [GU]) toxicity rates after TMT are low and QoL is good [475, 496, 497]. A combined analysis of survivors from four RTOG trials with a median follow-up of 5.4 years showed that combined-modality therapy was associated with low rates of late grade 3 toxicity (5.7% GU and 1.9% GI). No late grade 4 toxicities or treatment-related deaths were recorded [496]. A retrospective study showed QoL to be good after TMT and in most domains better than after cystectomy, although prospective validations are needed [498]. One option to reduce side effects after TMT is the use of IMRT and image-guided radiotherapy (IGRT) [8, 9, 499].

A collaborative review came to the conclusion that data are accumulating, suggesting that bladder preservation with TMT leads to acceptable outcomes and therefore TMT may be considered a reasonable treatment option in well-selected patients as compared to RC [481]. Bladder preservation as an alternative to RC is generally reserved for patients with smaller solitary tumours, negative nodes, no extensive or multifocal CIS, no tumour-

related hydronephrosis, and good pre-treatment bladder function. Trimodality bladder-preserving treatment should also be considered in all patients with a contraindication for surgery, either a relative or absolute contraindication since the factors that determine fitness for surgery and chemoradiotherapy differ. There are no definitive contemporary data supporting the benefit of using neoadjuvant or adjuvant chemotherapy combined with chemoradiation. Patient selection is critical in achieving good outcomes [481]. Whether a node dissection should be performed before TMT as in RC remains unclear [8, 9].

A bladder-preserving trimodality strategy requires very close multidisciplinary cooperation [8, 9]. This was also highlighted by a Canadian group [500]. In Ontario between 1994 and 2008 only 10% (370/3,759) of patients with cystectomy had a pre-operative radiation oncology consultation, with high geographical variations. Independent factors associated with this consultation included advanced age ($p < 0.001$), greater comorbidity ($p < 0.001$) and earlier year of diagnosis ($p < 0.001$). A bladder-preserving trimodality strategy also requires a high level of patient compliance. Even if a patient has shown a clinical response to a trimodality bladder-preserving strategy, the bladder remains a potential source of recurrence, hence long-term life-long bladder monitoring is essential and patients should be counselled that this will be required.

7.5.4.1 Summary of evidence and guidelines for trimodality bladder-preserving treatment

Summary of evidence	**LE**
In a selected patient population, long-term survival rates of trimodality bladder-preserving treatment are comparable to those of early cystectomy.	2b

Recommendations	**Strength rating**
Offer surgical intervention or trimodality bladder-preserving treatments (TMT) to appropriate candidates as primary curative therapeutic approaches since they are more effective than radiotherapy alone.	Strong
Offer TMT as an alternative to selected, well-informed and compliant patients, especially for whom radical cystectomy is not an option or not acceptable.	Strong

*7.5.4.2 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]**

Consensus statement
Candidates for curative treatment, such as cystectomy or bladder preservation, should be clinically assessed by at least an oncologist, a urologist, a radiation oncologist (in case adjuvant radiotherapy or bladder preservation is considered) and a neutral HCP such as a specialist nurse.
An important determinant for patient eligibility in case of bladder-preserving treatment is absence of carcinoma *in situ*.
An important determinant for patient eligibility in case of bladder-preserving treatment is absence or presence of hydronephrosis.
When assessing patient eligibility for bladder preservation, the likelihood of successful debulking surgery should be taken into consideration (optimal debulking).
In case of bladder preservation with radiotherapy, combination with a radiosensitiser is always recommended to improve clinical outcomes, such as cisplatin, 5FU/TMC, carbogen/nicotinamide or gemcitabine.
Radiotherapy for bladder preservation should be performed with IMRT and IGRT to reduce side effects.
Dose escalation above standard radical doses to the primary site in case of bladder preservation, either by IMRT or by brachytherapy, is not recommended.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
HCP = healthcare professional; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; 5FU = 5-fluorouracil; MMC = mitomycin-C.

7.6 Adjuvant therapy

7.6.1 ***Role of adjuvant platinum-based chemotherapy***

Adjuvant chemotherapy after RC for patients with pT3/4 and/or LN positive (N+) disease without clinically detectable metastases (M0) is still under debate [488, 501]. The general benefits of adjuvant chemotherapy include:

- chemotherapy is administered after accurate pathological staging, therefore, treatment in patients at low risk for micrometastases is avoided;
- no delay in definitive surgical treatment.

The drawbacks of adjuvant chemotherapy are:

- assessment of *in vivo* chemosensitivity of the tumour is not possible and overtreatment is an unavoidable problem;
- delay of or intolerability to chemotherapy, due to post-operative morbidity [502].

There is limited evidence from adequately conducted and accrued phase III RCTs in favour of the routine use of adjuvant chemotherapy [501, 503-508]. An individual patient data meta-analysis [503] of survival data from six RCTs of adjuvant chemotherapy [485, 509-512] included 491 patients (unpublished data from Otto *et al.*, were included in the analysis). All included trials suffered from significant methodological flaws including small sample size (underpowered), incomplete accrual, use of inadequate statistical methods and design flaws (irrelevant endpoints and failing to address salvage chemotherapy in case of relapse or metastases) [501]. In these trials, three or four cycles of CMV, cisplatin, cyclophosphamide, and adriamycin (CISCA), methotrexate, vinblastine, adriamycin or epirubicin, and cisplatin (MVA(E)C) and cisplatin and methotrexate (CM) were used [513], and one trial used cisplatin monotherapy [511]. The data were not convincing to support an unequivocal recommendation for the use of adjuvant chemotherapy. In 2014, this meta-analysis was updated with an additional three studies [505-507] resulting in the inclusion of 945 patients from nine trials [504]. None of the trials had fully accrued and individual patient data were not used in the analysis [504]. For one trial only an abstract was available at the time of the meta-analysis [506] and none of the included individual trials were significantly positive for OS in favour of adjuvant chemotherapy. In two of the trials more modern chemotherapy regimens were used (gemcitabine/cisplatin and paclitaxel/gemcitabine/cisplatin) [505, 506]. The HR for OS was 0.77 (95% CI: 0.59–0.99, p = 0.049) and for DFS 0.66 (95% CI: 0.45–0.91, p = 0.014) with a stronger impact on DFS in case of nodal positivity.

A retrospective cohort analysis including 3,974 patients after cystectomy and LND showed an OS benefit in high-risk subgroups (extravesical extension and nodal involvement) (HR: 0.75, CI: 0.62–0.90) [514]. A recent publication of the largest RCT (European Organisation for Research and Treatment of Cancer [EORTC] 30994), although not fully accrued, showed a significant improvement of PFS for immediate, compared with deferred, cisplatin-based chemotherapy (HR: 0.54, 95% CI: 0.4–0.73, p < 0.0001), but there was no significant OS benefit [515].

Furthermore, a large observational study including 5,653 patients with pathological T3–4 and/or pathological node-positive BC, treated between 2003 and 2006 compared the effectiveness of adjuvant chemotherapy vs. observation. Twenty-three percent of patients received adjuvant chemotherapy with a 5-year OS of 37% for the adjuvant arm vs. 29.1% (HR: 0.70, 95% CI: 0.64–0.76) in the observation group [516].

Another large retrospective analysis based on National Cancer Data Base including 15,397 patients with locally advanced (pT3/4) or LN-positive disease also demonstrated an OS benefit in patients with UC histology [517]. In patients with concomitant variant or pure variant histology, however, no benefit was found.

From the currently available evidence it is still unclear whether immediate adjuvant chemotherapy or chemotherapy at the time of relapse is superior, or if the two approaches are equivalent with respect to the endpoint of OS. The most recent meta-analysis from 2014 showed a therapeutic benefit of adjuvant chemotherapy, but the level of evidence of this review is still very low, with significant heterogeneity and methodological flaws in the only nine included trials [504]. Patients should be informed about potential chemotherapy options before RC, including neoadjuvant and adjuvant chemotherapy, and the limited evidence for adjuvant chemotherapy.

7.6.2 ***Role of adjuvant immunotherapy***

To determine the benefit of PD-1/PD-L1 checkpoint inhibitors, three phase III RCTs have evaluated checkpoint inhibitor monotherapy with atezolizumab, nivolumab or pembrolizumab in patients with muscle-invasive UC. The CheckMate 274 phase III multi-centre, double-blind, randomised, controlled trial of adjuvant nivolumab vs. placebo for up to 1 year in 709 patients with muscle-invasive UC (neoadjuvant cisplatin-based chemotherapy was allowed before trial entry) demonstrated a significant improvement in median DFS (20.8 months (95% CI:

16.5–27.6) with nivolumab and 10.8 months (95% CI: 8.3–13.9) with placebo). The percentage of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo (HR for disease recurrence or death, 0.70; 98.22% CI: 0.55–0.90; p < 0.001). Among patients with a PD-L1 expression level of ≥ 1%, the percentage of patients was 74.5% and 55.7%, respectively (HR: 0.55; 98.72% CI: 0.35–0.85; p < 0.001) [518]. The primary endpoint of DFS was not achieved in a multi-centre RCT of adjuvant atezolizumab vs. observation (IMvigor010) Median DFS was 19·4 months (95% CI: 15.9–24.8) with atezolizumab and 16.6 months (11.2–24.8) with observation (stratified HR: 0.89, 95% CI: 0.74–1.08, p = 0.24) [519]. A similarly designed trial of pembrolizumab in the adjuvant setting has completed accrual with results awaited. The FDA has approved nivolumab for adjuvant treatment of patients with UC who are at high risk of recurrence after undergoing surgery [520]. A promising report (see Marker section) has suggested for a potential role for ctDNA to guide the use of adjuvant IO for UC [223].

*7.6.3 **Summary of evidence and guidelines for adjuvant therapy***

Summary of evidence	LE
Adjuvant cisplatin-based chemotherapy for high-risk patients (pT3, 4 and/or or N+ M0) without neoadjuvant treatment can be associated with improvement in DFS and OS but trials are underpowered to adequately answer this question.	2a
To date, studies of immune checkpoint inhibitors in the adjuvant setting for patients with high-risk MIBC who have and have not received neoadjuvant chemotherapy have demonstrated conflicting results with the CheckMate 274 study demonstrating an improvement in DFS with adjuvant nivolumab and the IMvigor 010 study failing to show an improvement in DFS with adjuvant atezolizumab.	1b
Results for adjuvant treatment with immune-checkpoint inhibitors in high-risk MIBC are conflicting: nivolumab improved DFS (Checkmate 274) whereas atezolizumab did not (IMvigor 010).	1b
Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	2b

Recommendations	Strength rating
Offer adjuvant cisplatin-based combination chemotherapy to patients with pT3/4 and/or pN+ disease if no neoadjuvant chemotherapy has been given.	Strong
Discuss immunotherapy with nivolumab with selected patients with pT3/4 and/or pN+ disease not eligible for, or who declined, adjuvant cisplatin-based chemotherapy.	Weak

7.7 Metastatic disease

*7.7.1 **Introduction***

The treatment of metastatic UC had remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line treatment with cisplatin-based combinations demonstrating an OS benefit. In the past few years this longstanding paradigm has been challenged by several large studies investigating the benefit of immunotherapy using checkpoint inhibitors. Moreover, novel compounds including both targeted therapy and antibody-drug conjugates have been successfully tested and approved in later treatment lines.

*7.7.2 **First-line systemic therapy for metastatic disease***

In general, patients with untreated metastatic UC can be divided into three broad categories: fit for cisplatin-based chemotherapy, fit for carboplatin-based chemotherapy (but unfit for cisplatin) and unfit for any platinum-based chemotherapy.

Definitions: 'Fit for cisplatin, fit for carboplatin, unfit for any platinum-based chemotherapy'

An international survey among BC experts [521] was the basis for a consensus statement on how to classify patients unfit for cisplatin-based chemotherapy. At least one of the following criteria must be present: PS > 1; GFR ≤ 60 mL/min; grade ≥ 2 audiometric hearing loss; grade ≥ 2 peripheral neuropathy or New York Heart Association (NYHA) class III heart failure [522]. Around 50% of patients with BC are not eligible for cisplatin-based chemotherapy [522]. Renal function assessment is of utmost importance for treatment selection. Measuring GFR with radioisotopes (^{99}mTc DTPA or ^{51}Cr-EDTA) is recommended in equivocal cases.

Cisplatin has also been administered in patients with a lower GFR (40–60 mL/min) using different split-dose schedules. The respective studies were mostly small phase I and II trials in different settings (neoadjuvant and advanced disease) demonstrating that the use of split-dose cisplatin is feasible and appears

to result in encouraging efficacy [523-525]. However, no prospective RCT has compared split-dose cisplatin with conventional dosing.

Most patients that are deemed unfit for cisplatin are able to receive carboplatin-based chemotherapy. However, some patients are deemed unfit for any platinum-based chemotherapy, i.e. both cisplatin and carboplatin. Patient are unfit for any platinum-based chemotherapy in case of PS > 2, GFR < 30 mL/min or the combination of PS 2 and GFR < 60 mL/min since the outcome in this patient population is poor regardless of platinum-based treatment or not [526]. Patients with multiple comorbidities may also be poor candidates for platinum-based chemotherapy. Definitions of platinum-eligibility for first-line treatment of metastatic UC are summarised in Table 7.2.

Table 7.2: Definitions of platinum-eligibility for first-line treatment of metastatic urothelial carcinoma

Platinum-eligible		Platinum-ineligible
Cisplatin-eligible	**Carboplatin-eligible**	
ECOG PS 0-1 *and*	ECOG PS 2 *or* GFR 30–60 mL/min	Any of the following:
GFR > 50–60 mL/min *and*	or not fulfilling other cisplatin-eligibility criteria	GFR < 30mL/min
Audiometric hearing loss grade < 2 *and*		ECOG PS > 2
Peripheral neuropathy grade < 2 *and*		ECOG PS 2 *and* GFR < 60 mL/min
Cardiac insufficiency NYHA class < III		Comorbidites > Grade 2

ECOG = Eastern Cooperative Oncology Group; GFR = glomerular filtration rate; NYHA = New York Heart Association; PS = performance status.

7.7.2.1 First-line chemotherapy in patients fit for cisplatin

Cisplatin-containing combination chemotherapy has been the standard of care since the late 1980s demonstrating an OS of 12 to 14 months in different series (for a review see [527]). Methotrexate, vinblastine, adriamycin plus cisplatin and GC achieved survival of 14.8 and 13.8 months, respectively [528]. Overall response rates were 46% for MVAC and 49% for GC. The lower toxicity of GC [183] compared to standard MVAC has resulted in GC becoming the standard regimen.

Dose-dense MVAC combined with granulocyte colony-stimulating factor (G-CSF) is less toxic and more efficacious than standard MVAC in terms of, complete response (CR), and 2-year OS. However, there is no significant difference in median survival between the two regimens [529, 530]. Further intensification of treatment using paclitaxel, cisplatin and gemcitabine (PCG) triple regimen did not result in a significant improvement in OS in the intention-to-treat (ITT) population of a phase III RCT, comparing PCG to GC [531]. Similarly, the addition of the angiogenesis inhibitor bevacizumab to GC did not result in OS improvement [532].

The disease sites have an impact on long-term survival. In LN-only disease, 20.9% of patients were alive at five years compared to only 6.8% of patients with visceral metastases [528]. In the trials with long-term follow-up approximately 10-15% of patients with metastatic UC are alive at 5 years and longer, suggesting a sustained benefit from cisplatin-based chemotherapy in a minority of patients [528, 530].

Carboplatin-containing chemotherapy is not considered to be equivalent to cisplatin-based combinations, and should not be considered interchangeable or standard in patients fit for cisplatin. A comparative analysis of four randomised phase II trials of carboplatin vs. cisplatin combination chemotherapy demonstrated lower CR rates and shorter OS for the carboplatin arms [533]. Recently, a retrospective study highlighted the importance of applying cisplatin in cisplatin-eligible patients in order to maintain benefit [534].

7.7.2.2 First-line chemotherapy in patients fit for carboplatin (but unfit for cisplatin)

Up to 50% of patients are not fit for cisplatin-containing chemotherapy but most may be candidates for carboplatin [522]. The first randomised phase II/III trial in this setting was conducted by the EORTC and compared two carboplatin-containing regimens (methotrexate/carboplatin/vinblastine [M-CAVI] and gemcitabine/carboplatin [GemCarbo]) in patients unfit for cisplatin. The EORTC definitions for eligibility were GFR < 60 mL/min and/or PS 2. Severe acute toxicity was 13.6% with GemCarbo vs. 23% with M-CAVI, while the ORR was 42% for GemCarbo and 30% for M-CAVI, respectively [526]. Based on these results the combination of carboplatin and gemcitabine should be considered a standard of care in this patient group.

Combinations of gemcitabine and paclitaxel have been studied as first-line treatment and produced response rates between 38% and 60% but has never been tested in RCTs [535-537]. A randomised phase II trial assessed the efficacy and tolerability profile of two vinflunine-based regimens (vinflunine/gemcitabine vs. vinflunine/carboplatin). Both regimens showed equal ORR and OS with less haematologic toxicity for the combination of vinflunine/gemcitabine [538]. Non-platinum combination chemotherapy is nevertheless not recommended for first-line use in platinum-eligible patients.

The use of single-agent chemotherapy has been associated with varying response rates. Responses with single agents are usually short, complete responses are rare, and no long-term DFS/OS has been reported. It is not recommended for first-line treatment of metastatic UC.

7.7.2.3 Integration of immunotherapy in the first-line chemotherapy treatment of patients fit for platinum (cisplatin or carboplatin)

7.7.2.3.1 Immunotherapy combination approaches

In 2020, the results of three phase III trials have been published investigating the use of immunotherapy in the first-line setting for platinum-eligible patients. The first trial to report was IMvigor130 investigating the combination of the PD-L1 inhibitor atezolizumab plus platinum-gemcitabine chemotherapy vs. chemotherapy plus placebo vs. atezolizumab alone [539]. The primary endpoint of PFS benefit for the combination vs. chemotherapy alone in the ITT group was reached (8.2 months vs. 6.3 months [HR: 0.82, 95% CI: 0.70–0.96; one-sided, p = 0.007]) while OS was not significant at the interim analysis after a median follow-up of 11.8 months. The small PFS benefit in the absence of an OS benefit has raised questions of its clinical significance. Due to the sequential testing design, the comparison of chemotherapy vs. atezolizumab alone has not yet been formally performed.

The KEYNOTE 361 study had a very similar design using the PD-1 inhibitor pembrolizumab plus platinum-gemcitabine vs. chemotherapy plus placebo vs. pembrolizumab alone. The results of the primary endpoints of PFS and OS for the comparison of pembrolizumab plus chemotherapy vs. chemotherapy plus placebo in the ITT population showed no benefit for the combination [540].

DANUBE compared the immunotherapy combination (IO-IO) of CTLA-4 inhibitor tremelimumab and PD-L1 inhibitor durvalumab with chemotherapy alone or durvalumab alone [541]. The co-primary endpoint of improved OS for the IO-IO combination vs. chemotherapy was not reached in the ITT group nor was the OS improved for durvalumab monotherapy vs. chemotherapy in the PD-L1-positive population.

In conclusion, these three trials do not support the use of combination of PD-1/L1 checkpoint inhibitors plus chemotherapy or the IO-IO combination as first-line treatment.

7.7.2.3.2 Use of first-line single-agent immunotherapy in patients unfit for cisplatinum-based chemotherapy

Based on the results of two single-arm phase II trials [542, 543] the checkpoint inhibitors pembrolizumab and atezolizumab have been approved by the U.S. FDA and the European Medicines Agency (EMA) for first-line treatment in cisplatin-unfit patients in case of positive PD-L1 status. PD-L1 positivity for use of pembrolizumab is defined by immunohistochemistry as a CPS of ≥ 10 using the Dako 22C33 platform and for atezolizumab as positivity of ≥ 5% tumour-infiltrating immune cells using Ventana SP142.

Pembrolizumab was tested in 370 patients with advanced or metastatic UC ineligible for cisplatin, showing an ORR of 29% and CR in 7% of patients [542]. Atezolizumab was evaluated in the same patient population in a phase II trial (n = 119) showing an ORR of 23% with 9% of patients achieving CR [543].

The trials IMvigor 130, Keynote 361 and DANUBE all included an experimental arm with immunotherapy alone using atezolizumab, pembrolizumab and durvalumab, respectively [539-541]. No benefit in terms of PFS or OS for the use of single-agent immunotherapy compared to platinum-based chemotherapy was found. The combination of carboplatin/gemcitabine therefore is considered the preferred first-line treatment choice for patients ineligible for cisplatin but eligible for carboplatin.

7.7.2.3.3 Switch maintenance with immunotherapy after platinum-based chemotherapy

A randomised phase II trial evaluated switch maintenance treatment with pembrolizumab in patients achieving at least stable disease on platinum-based first-line chemotherapy. The primary endpoint of PFS was met (5.4 months vs. 3.0 months, HR: 0.65, p = 0.04) but not the secondary endpoint of OS (22 months vs. 18.7 months, HR: 0.91, 95% CI: 0.52–1.59) [544].

The JAVELIN Bladder 100 study investigated the impact of switch maintenance with the PD-L1 inhibitor avelumab after initial treatment with platinum-gemcitabine chemotherapy. Patients achieving at least stable disease or better after 4–6 cycles of platinum-gemcitabine were randomised to avelumab or best supportive care (BSC). Overall survival was the primary endpoint which improved to 21.4 months with avelumab compared to 14.3 months with BSC (HR: 0.69, 95% CI: 0.56–0.86; p < 0.001). Of patients who

discontinued BSC and received subsequent treatment 53% received immunotherapy. Immune-related AEs occurred in 29% of all patients and 7% experienced grade 3 complications [545].

In conclusion, maintenance IO with avelumab is a standard of care for all patients with disease stabilisation on first-line platinum-based chemotherapy.

7.7.2.4 Treatment of patients unfit for any platinum-based chemotherapy

Very limited data exist regarding the optimal treatment for this patient population which is characterised by severely impaired PS (PS > 2) and/or severely impaired renal function (GFR < 30 mL/min). Historically, the outcome in this patient group has been poor. Best supportive care has often been chosen instead of systemic therapy. Most trials evaluating alternative treatment options to cisplatinum-based chemotherapy did not focus specifically on this patient population thereby making interpretation of data difficult. The FDA (but not EMA) has approved pembrolizumab and atezolizumab as first-line treatment for patients not fit to receive any platinum-based chemotherapy regardless of PD-L1 status based on the results of two single-arm phase II trials [542, 543]. These trials have not reported how many patients were unfit for any platinum-based chemotherapy.

*7.7.3 **Second-line systemic therapy for metastatic disease***

7.7.3.1 Second-line chemotherapy

Second-line chemotherapy data are highly variable and mainly derive from small single-arm phase II trials apart from a single phase III RCT. A reasonable strategy has been to re-challenge former platinum-sensitive patients if progression occurred at least six to twelve months after first-line platinum-based combination chemotherapy. Second-line response rates of single-agent treatment with paclitaxel (weekly), docetaxel, gemcitabine, nab-paclitaxel, oxaliplatin, ifosfamide, topotecan, pemetrexed, lapatinib, gefitinib and bortezomib have ranged between 0% and 28% in small phase II trials [546, 547].

The paclitaxel/gemcitabine combination has shown good response rates in small single-arm studies but no adequate phase III RCT has been conducted [548, 549].

Vinflunine was tested in a phase III RCT and compared against BSC in patients progressing after first-line treatment with platinum-based chemotherapy [550]. The results showed a very modest ORR (8.6%), a clinical benefit with a favourable safety profile and a survival benefit, which was however only statistically significant in the eligible patient population (not in the ITT population).

A randomised phase III trial evaluated the addition of the angiogenesis inhibitor ramucirumab to docetaxel chemotherapy vs. docetaxel alone, which resulted in improved PFS (4.1 vs. 2.8 months) and higher response rates (24.5% vs. 14%) but no OS benefit was achieved [551, 552].

7.7.3.2 Second-line immunotherapy for platinum-pre-treated patients

The immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab have demonstrated similar efficacy and safety in patients progressing during, or after, previous platinum-based chemotherapy in phase I, II and III trials.

Pembrolizumab demonstrated a significant OS Improvement as second-line treatment in a phase III RCT leading to EMA and FDA approval. Patients (n = 542) were randomised to receive either pembrolizumab monotherapy or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS with pembrolizumab was 10.3 months (95% CI: 8.0–11.8) vs. 7.4 months (95% CI: 6.1–8.3) with chemotherapy (HR 0.73, 95% CI: 0.59–0.91, p = 0.002) independent of PD-L1 expression levels [553].

Atezolizumab was the first checkpoint inhibitor approved by FDA for metastatic UC based on the results of phase I and II trials [215, 554] The phase III RCT (IMvigor211) included 931 patients comparing atezolizumab with second-line chemotherapy (paclitaxel, docetaxel or vinflunine) did not meet its primary endpoint of improved OS for patients with high PD-L1 expression with 11.1 months (atezolizumab) vs. 10.6 (chemotherapy) months (stratified HR: 0.87, 95% CI: 0.63–1.21, p = 0.41) [555].

The PD-1 inhibitor nivolumab was approved by the FDA based on the results of a single-arm phase II trial (CheckMate 275), enrolling 270 platinum pre-treated patients. The primary endpoint of ORR was 19.6%, and OS was 8.74 months for the entire group [556].

Based on level 1 evidence from a RCT, pembrolizumab has emerged in clinic as the preferred standard of care immunotherapy in the second-line setting.

7.7.3.3 Side-effect profile of immunotherapy

Checkpoint inhibitors including PD-1 or PD-L1 antibodies and CTLA-4 antibodies have a distinct side-effect profile associated with their mechanism of action leading to enhanced immune system activity. These AEs

can affect any organ in the body leading to mild, moderate or severe side effects. The most common organs affected are the skin, GI tract, liver, lung, thyroid, adrenal and pituitary gland. Other systems that may be affected include musculoskeletal, renal, nervous, haematologic, ocular and cardiovascular system. Any change during immunotherapy treatment should raise suspicion about a possible relation to the treatment. The nature of immune-related AEs has been very well characterised and published [557]. The timely and appropriate treatment of immune-related side effects is crucial to achieve optimal benefit from the treatment while maintaining safety. Clear guidelines for side-effect management have been published [558]. Immunotherapy treatment should be applied and supervised by trained clinicians only to ensure early side effect recognition and treatment. In case of interruption of immunotherapy, re-challenge will require close monitoring for AEs [559].

*7.7.4 **Integration of novel agents***

7.7.4.1 Antibody drug conjugates

The first antibody drug conjugate to report encouraging data was enfortumab vedotin, an antibody-drug conjugate targeting Nectin-4, a cell adhesion molecule which is highly expressed in UC conjugated to monomethyl auristatin E (MMAE). A phase-II single-arm study (EV-201) in 125 patients previously treated with platinum chemotherapy and checkpoint inhibition showed a confirmed objective response rate of 44%, including 12% complete responses [560]. This data led to accelerated FDA and EMA approval for enfortumab vedotin in locally advanced or metastatic UC patients who have previously received a PD-1 or PD-L1 inhibitor, and platinum-containing chemotherapy [561, 562]. Another cohort of the same EV-201 trial demonstrated similar promising results in a cohort of 91 patients that were cisplatin-ineligible and had received prior IO [563]. A phase III RCT (n = 608) comparing enfortumab vedotin with single-agent chemotherapy after prior platinum chemotherapy and checkpoint inhibitor immunotherapy demonstrated significant survival benefit of almost 4 months (12.88 months vs. 8.97 months; HR 0.7, 95% CI: 0.56–0.89) [564]. The most common treatment-related AEs included alopecia (45%), peripheral neuropathy (34%), fatigue (31%, 7.4% ≥ grade 3), decreased appetite (31%), diarrhoea (24%), nausea (23%). and skin rash (16%, 7.4% ≥ grade 3).

Preliminary results of the combination of enfortumab vedotin and pembrolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced/metastatic UC have been reported resulting in ORR of 73.3% with 15.6% complete responses [565]. Treatment-related AEs of interest included any rash (48% all grade, 11% ≥ grade 3) and any peripheral neuropathy (50% all grade, 3% ≥ grade 3). This combination is currently under investigation in a phase III trial in the first-line setting for platinum-eligible patients (EV-302).

Based on these results enfortumab vedotin has been FDA approved for patients who have received prior platinum-containing chemotherapy and prior IO with PD-1 or PD-L1 inhibitor as well as for cisplatin-ineligible patients who have received one or more prior lines of therapy.

Another new and also promising antibody drug conjugate is sacituzumab govitecan, consisting of a humanised monoclonal antibody targeting trophoblast cell surface antigen 2 (Trop-2) conjugated to SN-38, the active metabolite of irinotecan. Sacituzumab govitecan was tested in 113 platinum and IO pre-treated metastatic UC (mUC) patients [560] and achieved an ORR of 27% and a total of 77% had a decrease in measurable disease, median PFS was 5.4 months and median OS 10.9 months [566]. Side effects consisted of haematological toxicities (neutropenia 34% ≥ grade 3; febrile neutropenia 10% ≥ grade 3), fatigue (52%), alopecia (47%), nausea (60%), diarrhea (65%, 10% ≥ grade 3) and decreased appetite (36%) [566]. Sacituzumab govitecan has received accelerated FDA approval for metastatic UC with prior platinum and IO pre-treatment. Several trials using sacituzumab govitecan as monotherapy or in combinations are ongoing.

7.7.4.2 FGFR inhibition

Genomic profiling of UC has revealed common potentially actionable genomic alterations including alterations in *FGFR* [567]. Erdafitinib is a pan-*FGFR* tyrosine kinase inhibitor and the first FDA-approved targeted therapy for mUC with susceptible *FGFR2/3* alterations following platinum-containing chemotherapy. The phase II trial of erdafitinib included 99 patients whose tumour harboured an *FGFR3* mutation or *FGFR2/3* fusion and who had disease progression following chemotherapy [213]. The confirmed ORR was 40% and an additional 39% of patients had stable disease. A total of 22 patients had previously received immunotherapy with only one patient achieving a response, yet the response rate for erdafitinib for this subgroup was 59%. At a median follow-up of 24 months, the median PFS was 5.5 months (95% CI: 4.0–6.0) and the median OS was 11.3 months (95% CI: 9.7–15.2) [213]. Treatment-related AEs of ≥ grade 3 occurred in 46% of patients. Common AEs of ≥ grade 3 were hyponatraemia (11%), stomatitis (10%), and asthenia (7%) and 13 patients discontinued erdafitinib due to AEs, including retinal pigment epithelial detachment, hand-foot syndrome, dry mouth, and skin/nail events. In addition to erdafitinib, several other *FGFR* inhibitors are being evaluated including infigratinib which

has demonstrated promising activity [214]. The increased identification of *FGFR3* mutations/fusion has led to several ongoing trials with different agents and combination in different disease settings.

*7.7.5 **Current status of predictive biomarkers***

The most important advance in recent years has been the recognition of alterations in *FGFR3* including mutations and gene fusions as a predictive marker for response to *FGFR* inhibitors [213]. It is rrecommended to screen mUC patients ideally at diagnosis of metastatic disease for *FGFR3* alterations to plan optimal treatment including trials.

Many efforts have focused on markers for predicting response to immune checkpoint inhibition. Programmed death-ligand 1 expression by immunohistochemistry has been evaluated in many studies with mixed and, so far, inconclusive results. This may in part be related to the use of different antibodies and various scoring systems evaluating different compartments i.e., tumour cells, immune cells, or both. A major limitation of PD-L1 staining relates to the significant proportion of PD-L1-negative patients that respond to immune checkpoint blockade. The predictive value of PD-L1 was not confirmed in large phase III trials evaluating the integration of immunotherapy in the first-line setting for mUC [539-541]. At present, the only indication for PD-L1 testing in mUC is dictated by current the FDA and EMA approvals and relates to the potential use of immune checkpoint inhibitors as first-line monotherapy in patients unfit for cisplatin-containing chemotherapy.

Another biomarker that has been evaluated for predicting response to immunotherapy is high TMB [217]. Neoantigen burden and TMB have been associated with response to immune checkpoint blockade in several malignancies. High TMB has been associated with response to immune checkpoint inhibitors in metastatic UC in small single arm trials [215, 218] but was not confirmed so far in RCTs. Other markers that have been evaluated in predicting response to immune checkpoint inhibitors include molecular subtypes, CD8 expression by immunohistochemistry and other immune gene cell signatures. Recent work has focused on the importance of stroma including the role of TGFs in predicting response to immune checkpoint blockade [221, 222].

In conclusion, apart from *FGFR3* alterations, there are currently no further validated predictive molecular markers that are routinely used in clinical practice.

*7.7.6 **Special situations***

7.7.6.1 Impact of prior neoadjuvant/adjuvant therapy on treatment sequence

Peri-operative systemic treatment is increasingly used in UC including cisplatin-based chemotherapy in the neoadjuvant setting for BC and adjuvant platinum-based chemotherapy for upper tract UC [568]. Many ongoing phase III trials investigate the use of immunotherapy in this setting as well. So far, one trial has reported a significant DFS benefit for adjuvant treatment with nivolumab compared with placebo whereas one trial reported no significant benefit using atezolizumab vs. placebo in the same setting whilst another trial reported negative findings [518, 519]. It is expected that an increased number of patients with metastatic UC will have received pre-treatment with platinum and/or immunotherapy agents. No prospective trials have investigated the treatment of such patients. The choice of treatment in these patients depends on the applied peri-operative treatment and the time until relapse. If at least 12 months have passed since the end of peri-operative treatment the same systemic treatment as in treatment-naïve patients is recommended. To help prevent early relapse within 12 months the peri-operative systemic therapy has to be taken into account when planning further treatment.

7.7.6.2 Systemic treatment of metastatic disease with histology other than pure urothelial carcinoma

Pure urothelial carcinoma (PUC) represents the predominant histology in over 90% of patients with mUC. Variant histologies (e.g. micropapillary, nested, sarcomatoid) and divergent differentiation (e.g. SCC, adenocarcinoma) can be found in addition to PUC in up to 33% of patients. Such patients were often excluded from large phase II and phase III trials and therefore the knowledge about the best management of such patients is limited. The respective literature was reviewed recently [68] and an expert Delphi survey and consensus conference provided guidance [9]. In case of predominant PUC it is recommended to treat patients with mixed histology the same way as patients with PUC histology. Patients with predominant non-urothelial differentiation such as small cell neuroendocrine carcinoma, urachal adenocarcinoma, SCC and adenocarcinoma should be treated individually.

*7.7.7 **Treatment of patients with bone metastases***

The prevalence of metastatic bone disease (MBD) in patients with advanced/metastatic UC is 30–40% [569]. Skeletal complications due to MBD have a detrimental effect on pain and QoL and are also associated with increased mortality [570]. Bisphosphonates such as zoledronic acid reduce and delay skeletal-related events (SREs) due to bone metastases by inhibiting bone resorption, as shown in a small pilot study [571].

Denosumab, a fully human monoclonal antibody that binds to and neutralises RANKL (receptor activator of nuclear factor κB ligand), was shown to be non-inferior to zoledronic acid in preventing or delaying SREs in patients with solid tumours and advanced MBD, including patients with UC [572]. Patients with MBD, irrespective of the cancer type, should be considered for bone-targeted treatment [570].

Patients treated with zoledronic acid or denosumab should be informed about possible side effects including osteonecrosis of the jaw and hypocalcaemia. Supplementation with calcium and vitamin D is mandatory. Dosing regimens of zoledronic acid should follow regulatory recommendations and have to be adjusted according to pre-existing medical conditions, especially renal function [573]. For denosumab, no dose adjustments are required for variations in renal function.

*7.7.8 **Summary: treatment algorithm for metastatic urothelial cancer update 2021***

Figure 7.2 summarises the treatment algorithm for metastatic BC based on the evidence discussed in the text above.

Patients with treatment-naïve mUC are grouped according to platinum-eligibility based on clear definitions. In general, first-line treatment consists of platinum-based chemotherapy in which cisplatin is to be preferred to carboplatin. Patients who are cisplatin-ineligible but carboplatin-eligible should receive carboplatin-gemcitabine combination chemotherapy. In case of positive PD-L1 status, treatment with checkpoint inhibitors (atezolizumab or pembrolizumab) could be an alternative option.

Patients unfit for both cisplatin and carboplatin (platinum-unfit) can be considered for immunotherapy (FDA approved irrespective of PD-L1 status, EMA approved only for PD-L1 positive patients) or receive BSC.

In cases of disease stabilization on platinum-based chemotherapy switch, maintenance treatment with IO (avelumab) is recommended. Alternatively, patients can be followed closely and receive second-line immunotherapy at the time of progression (pembrolizumab).

It is recommended to determine *FGFR* mutation status before deciding about second-line treatment. Patients with *FGFR3* mutations are candidates for *FGFR* inhibitor treatment. Enfortumab vedotin therapy is the new standard in case of progression after platinum chemotherapy and IO but has not yet been approved in Europe. The optimal sequence of novel agents and potential combinations are the subject of many ongoing trials. It is generally recommended to treat patients within ongoing clinical trials.

*7.7.9 **Summary of evidence and guidelines for metastatic disease***

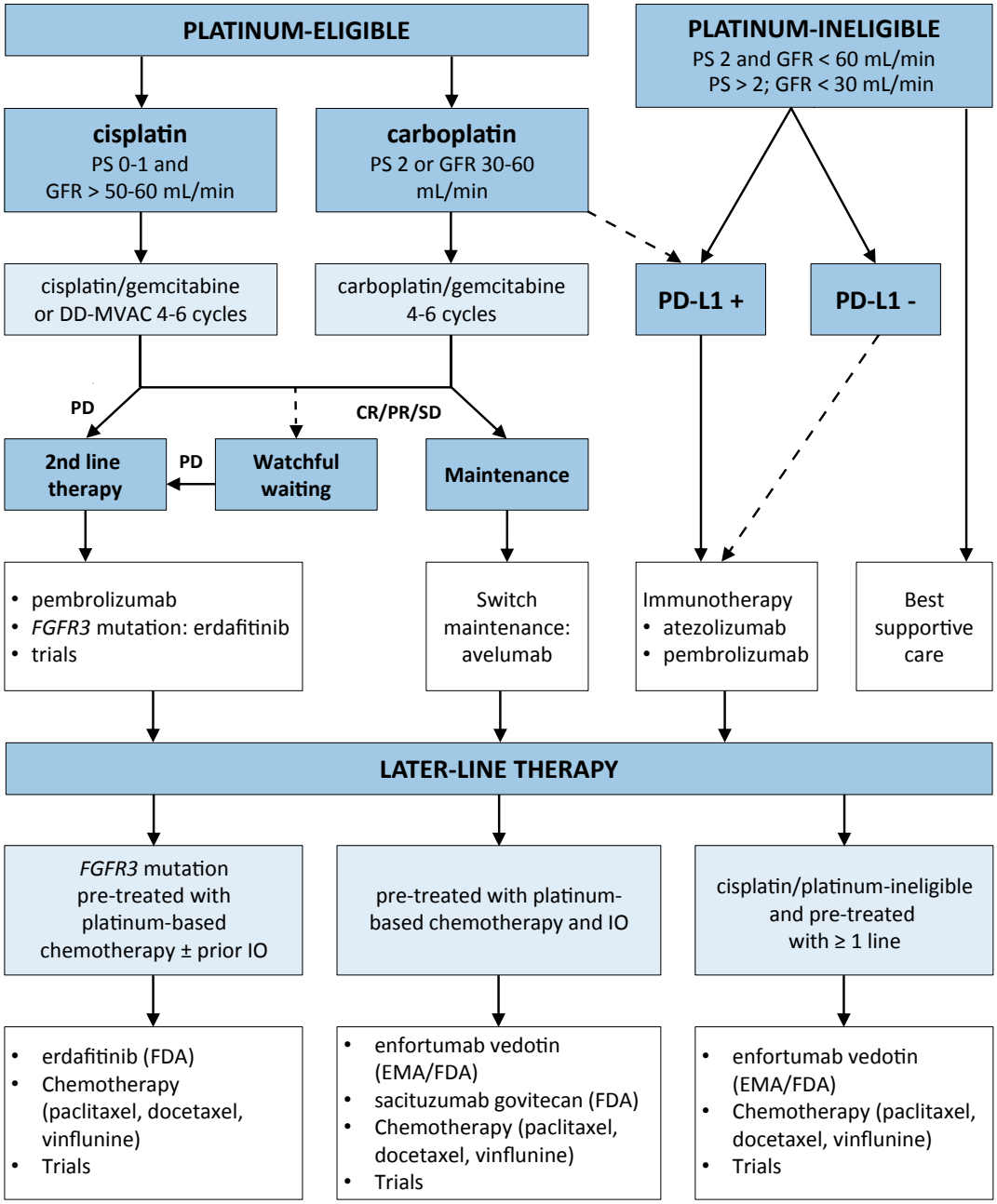
Summary of evidence	**LE**
In a first-line setting, PS and the presence or absence of visceral metastases are independent prognostic factors for survival.	1b
In a second-line setting, negative prognostic factors are: liver metastasis, PS ≥ 1 and low haemoglobin (< 10 g/dL).	1b
Cisplatin-containing combination chemotherapy can achieve median survival of up to 14 months, with long-term DFS reported in ~15% of patients with nodal disease and good PS.	1b
Single-agent chemotherapy provides low response rates of usually short duration.	2a
Carboplatin combination chemotherapy is less effective than cisplatin-based chemotherapy in terms of complete response and survival.	2a
There is no defined standard therapy for platinum chemotherapy-unfit patients with advanced or metastatic UC.	2b
Post-chemotherapy surgery after partial or complete response may contribute to long-term DFS in highly selected patients.	3
Zoledronic acid and denosumab have been approved for supportive treatment in case of bone metastases of all cancer types including UC, as they reduce and delay skeletal related events.	1b
PD-1 inhibitor pembrolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy based on the results of a phase III trial.	1b
Enfortumab vedotin after prior platinum chemotherapy and checkpoint inhibitor immunotherapy has demonstrated a significant survival benefit as compared to chemotherapy.	1b
PD-L1 inhibitor atezolizumab is approved for patients with advanced or metastatic UC unfit for cisplatin-based chemotherapy in case of high PD-1 expression defined as tumour-infiltrating immune cells covering ≥ 5% of the tumour area using the SP142 assay.	1b

PD-1 inhibitor pembrolizumab is approved for patients with advanced or metastatic UC unfit for any platinum-based chemotherapy in case of high PD-1 expression defined as CPS of ≥ 10 using the Dako 22C33 platform (EMA; FDA approval independent of PD-1 status).	1b
The combination of chemotherapy plus pembrolizumab or atezolizumab and the combination of durvalumab and tremelimumab have not demonstrated OS survival benefit compared to platinum-based chemotherapy alone.	1b
Switch maintenance with the PD-L1 inhibitor avelumab has demonstrated significant OS benefit in patients achieving at least stable disease on first-line platinum-based chemotherapy.	1b

Recommendations	**Strength rating**
First-line treatment for platinum-fit patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
In patients unfit for cisplatin but fit for carboplatin, use the combination of carboplatin and gemcitabine.	Strong
In patients achieving stable disease, or better, after first-line platinum-based chemotherapy, use maintenance treatment with PD-L1 inhibitor avelumab.	Strong
First-line treatment in patients unfit for platinum-based chemotherapy	
Consider checkpoint inhibitors pembrolizumab or atezolizumab in case of high PD-1 expression (for definitions see text).	Weak
Second-line treatment	
Offer checkpoint inhibitor pembrolizumab to patients progressing during, or after, platinum-based combination chemotherapy for metastatic disease.	Strong
Further treatment after platinum- and immunotherapy	
Offer antibody drug conjugate enfortumab vedotin as monotherapy to patients with advanced or metastatic UC pre-treated with platinum and immunotherapy.	Strong
Offer treatment in clinical trials testing novel drugs (e.g. sacituzumab govitecan); or in case of patients with *FGFR3* alterations, *FGFR* tyrosine kinase inhibitors.	Strong
Evaluate for *FGFR2/3* genetic alterations for the potential use of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma who have progressed following platinum-containing chemotherapy (including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy).	Weak

GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptor; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin.

Figure 7.2: Flow chart for the management of metastatic urothelial cancer*



**Treatment within clinical trials is highly encouraged.*
BSC = best supportive care; CR = complete response; DD-MVAC = dose dense methotrexate vinblastine doxorubicin cisplatin; EMA = European Medicines Agency; EV = enfortumab vedotin; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; GFR = glomerular filtration rate; IO = immunotherapy; PR = partial response; PS = performance status; SD = stable disease.

7.8 Quality of life

7.8.1 Introduction

The evaluation of HRQoL considers physical, psychological, emotional and social functioning. Several questionnaires have been validated for assessing HRQoL in patients with BC, including FACT-G [574], EORTC QLQ-C30 [575], EORTC QLQ-BLM30 [575], SF-36 [576] and recently the BCI questionnaire [577]. In spite of these validated questionnaires, there is heterogeneity in the measurements used to assess sexual health. A health questionnaire that covers the entire range of sexual health in bladder cancer patients is currently lacking [578]. In patients with bladder cancer, the overall HRQoL is lower compared to the general population and patients with other common pelvic cancers, independent of therapy received and disease stage [579].

In patients with MIBC, HRQoL appears to decline, particularly in the physical and social functioning domains [580]. Several questionnaires have been validated for assessing HRQoL in patients with BC, including

FACT (Functional Assessment of Cancer Therapy)-G [574], EORTC QLQ-C30 [575], EORTC QLQ-BLM (MIBC module) [575], and SF (Short Form)-36 [576, 581] and recently the BCI questionnaire specifically designed and validated for BC patients [577].

*7.8.2 **Neoadjuvant chemotherapy***

The impact of NAC on patient-reported outcomes (using EORTC QLQ questionnaires) was investigated by Feuerstein *et al.* [582]. A propensity-matched analysis of 101 patients who completed NAC and 54 patients who did not undergo NAC, showed no negative effect of NAC on patient-reported outcomes prior to RC. Recently, HRQoL data from two RCTs have been published [497, 583]. Huddart *et al.,* analysed the subset of patients within the BC2001 trial who underwent NAC prior to (chemo)radiation. Using the FACT-BL questionnaire, no detrimental impact of NAC on HRQoL was observed [497]. Kitamura *et al.*, reported on 64 patients included in the JCOG0209 study who underwent NAC (MVAC vs. MVAC and RC). An overall decline on HRQoL was reported directly following NAC using the FACT-BL questionnaire. However, no difference in HRQoL was observed after the consolidating RC.

*7.8.3 **Radical cystectomy and urinary diversion***

Two systematic reviews and meta-analyses focused on HRQoL after RC and urinary diversion [381, 584].

Yang *et al.*, compared HRQoL of incontinent and continent urinary diversions (all types) including 29 studies (n = 3,754) of which 9 had a prospective design (one of which was randomised) [381]. Only three studies reported HRQoL data both pre- and post-operatively. In these three studies, an initial deterioration in overall HRQoL was reported but general health, functional and emotional domains at 12 months post-surgery were equal or better than baseline. After 12 months, the HRQoL benefits diminished in all domains. Overall, no difference in HRQoL between continent and incontinent urinary diversion was reported although an ileal conduit may confer a small physical health benefit [584].

Cerruto *et al.*, reported HRQoL comparing ileal conduit with orthotopic neobladder reconstruction [584]. A pooled analysis was performed including 18 studies (n = 1,553) of which the vast majority were retrospective studies. The analysis showed no statistical significant difference in overall HRQoL, but methodological limitations need to be considered.

Clifford *et al.*, prospectively evaluated continence outcomes in male patients undergoing orthotopic neobladder diversion [585]. Day-time continence increased from 59% at less than three months post-operatively to 92% after 12 to 18 months. Night-time continence increased from 28% at less than three months post-operatively to 51% after 18 to 36 months. Also of interest is the urinary bother in females with an orthotopic neobladder. Bartsch and co-workers reported day-time and night-time continence rates of 70.4% and 64.8%, respectively, in 56 female neobladder patients. Thirty-five patients (62.5%) performed clean intermittent catheterisation, which is much worse when compared to male neobladder patients. Moreover, patients with non-organ-confined disease (p = 0.04) and patients with a college degree (p = 0.001) showed worse outcomes on HRQoL scores [586].

Altogether, there is no superior type of urinary diversion in terms of overall HRQoL but it is rather a result of proper patient selection. An older and isolated patient is probably better served with an ileal conduit, whereas a younger patient with a higher level of interest in body image and sexuality is better off with an orthotopic diversion. The patient's choice is the key to the selection of reconstruction method [381].

A number of RCTs comparing ORC with RARC (with either intra- or extracorporeal urinary diversion) have reported their HRQoL data [375, 376, 587, 588]. All studies reported no statistical significant difference in HRQoL outcomes between surgical techniques.

*7.8.4 **Bladder-sparing trimodality therapy***

The only HRQoL data in bladder sparing treatment collected in a RCT setting was published by Huddart *et al.* [497]. The primary endpoint was the change in the Bladder Cancer Subscale (BLCS), as part of the FACT-BL questionnaire, at one year post-treatment. Questionnaire return rate at one and five years was 70% and 60%, respectively. The remaining patients did mostly not respond as a result of recurrence or RC. A reduction in HRQoL was seen in the majority of the domains immediately following RT, however, in most patients the HRQoL scores returned to baseline 6 months after RT and maintained at this level for five years. Approximately 33% of patients reported persistent lower Bladder Cancer Subscale scores after five years. Addition of chemotherapy did not affect the HRQoL outcomes.

7.8.5 Non-curative or metastatic bladder cancer

In non-curative or metastatic BC, HRQoL is reduced because of associated micturition problems, bleeding, pain and therefore disturbance of social and sexual life [589]. Beneficial impact of palliative surgery [590], RT [591], and/or chemotherapy on bladder-related symptoms have been described [592].

A HRQoL analysis was performed in platinum-refractory patients who were randomised to pembrolizumab vs. another line of chemotherapy (KEYNOTE-45 trial) [593]. It was reported that patients treated with pembrolizumab had stable or improved global health status/QoL, whereas those treated with investigators' choice of chemotherapy experienced declines in global health [593].

7.8.6 Summary of evidence and recommendations for health-related quality of life

Summary of evidence	LE
Compared to non-cancer controls, the diagnosis and treatment of BC has a negative impact on HRQoL.	2a
There is no distinct difference in overall QoL between patients with continent or incontinent diversion.	2a
In patients with MIBC treated with RC, overall HRQoL declines immediately after treatment and recovers to baseline at 12 months post-operatively.	1a
HRQoL data are comparable for RARC (with either intracorporeal or extracorporeal urinary diversion) and ORC.	1b
In patients with MIBC treated with RT, overall HRQoL declines immediately after treatment. In most patients, overall HRQoL then recovers to baseline at 6 months and maintains at this level to 5 years.	1b
In patients with MIBC treated with radiotherapy, concomitant chemotherapy or neoadjuvant chemotherapy has no significant impact on HRQoL.	1b
In patients with platinum-refractory advanced UC, pembrolizumab may be superior in terms of HRQoL compared to another line of chemotherapy.	1b

Recommendations	Strength rating
Use validated questionnaires to assess health-related quality of life in patients with muscle-invasive bladder cancer.	Strong
Discuss the type of urinary diversion taking into account a patient preference, existing comorbidities, tumour variables and coping abilities.	Strong

8. FOLLOW-UP

8.1 Follow-up in muscle invasive bladder cancer

An appropriate schedule for disease monitoring should be based on natural timing of recurrence; probability and site of recurrence; functional monitoring after urinary diversion and the potential available management options [594].

Nomograms on CSS following RC have been developed and externally validated, but their wider use cannot be recommended until further data become available [595, 596].

Current surveillance protocols are based on patterns of recurrence drawn from retrospective series only. Combining this data is not possible since most retrospective studies use different follow-up regimens and imaging techniques. Additionally, reports of asymptomatic recurrences diagnosed during routine oncological follow-up and results from retrospective studies are contradictory [597-599]. From the Volkmer B, *et al.*, series of 1,270 RC patients, no differences in OS were observed between asymptomatic and symptomatic recurrences [598]. Conversely, in the Giannarini, *et al.*, series of 479 patients; those with recurrences detected during routine follow-up (especially in the lungs) and with secondary urothelial tumours as the site of recurrence, had a slightly higher survival [597]. Boorjian, *et al.*, included 1,599 RC patients in their series, with 77% symptomatic recurrences. On multivariate analysis, patients who were symptomatic at recurrence had a 60% increased risk of death as compared to asymptomatic patients [599].

However, at this time, no data from prospective trials demonstrating the potential benefit of early detection of recurrent disease and its impact on OS are available [600].

8.2 Site of recurrence

8.2.1 ***Local recurrence***

Local recurrence takes place in the soft tissues of the original surgical site or in LNs. Contemporary cystectomy has a 5–15% probability of pelvic recurrence which usually occurs during the first 24 months, most often within 6 to 18 months after surgery. However, late recurrences can occur up to five years after RC. Risk factors described are pathological stage, LNs, positive margins, extent of LND and peri-operative chemotherapy [601].

Patients generally have a poor prognosis after pelvic recurrence. Even with treatment, median survival ranges from four to eight months following diagnosis. Definitive therapy can prolong survival, but mostly provides significant palliation of symptoms. Trimodality management generally involves a combination of chemotherapy, radiation and surgery [600].

8.2.2 ***Distant recurrence***

Distant recurrence is seen in up to 50% of patients treated with RC for MIBC. As with local recurrence, pathological stage and nodal involvement are risk factors [602]. Systemic recurrence is more common in locally advanced disease (pT3/4), ranging from 32 to 62%, and in patients with LN involvement (range 52–70%) [603].

The most likely sites for distant recurrence are LNs, lungs, liver and bone. Nearly 90% of distant recurrences appear within the first three years after RC, mainly in the first two years, although late recurrence has been described after more than 10 years. Median survival of patients with progressive disease treated with platinum-based chemotherapy is 9–26 months [604-606]. However, longer survival (28–33% at 5 years) has been reported in patients with minimal metastatic disease undergoing trimodality management, including metastasectomy [607, 608].

8.2.3 ***Urothelial recurrences***

After RC, the incidence of new urethral tumours was 4.4% (1.3–13.7%). Risk factors for secondary urethral tumours are urethral malignancy in the prostatic urethra/prostate (in men) and bladder neck (in women). Orthotopic neobladder was associated with a significant lower risk of urethral tumours after RC (OR: 0.44) [609].

There is limited data, and agreement, about urethral follow-up, with some authors recommending routine surveillance with urethral wash and urine cytology and others doubting the need for routine urethral surveillance. However, there is a significant survival advantage in men with urethral recurrence diagnosed asymptomatically vs. symptomatically, so follow-up of the male urethra is indicated in patients at risk of urethral recurrence [600]. Treatment is influenced by local stage and grade of urethral occurrence. In urethral CIS, BCG instillations have success rates of 83% [610]. In invasive disease, urethrectomy should be performed if the urethra is the only site of disease; in case of distant disease, systemic chemotherapy is indicated [3].

Upper urinary tract UCs occur in 4–10% of cases and represent the most common sites of late recurrence (3-year DFS following RC) [611]. Median OS is 10–55 months, and 60–67% of patients die of metastatic disease [600]. A meta-analysis found that 38% of UTUC recurrence was diagnosed by follow-up investigations, whereas in the remaining 62%, diagnosis was based on symptoms. When urine cytology was used during surveillance, the rate of primary detection was 7% vs. 29.6% with UUT imaging. The meta-analysis concluded that patients with non-invasive cancer are twice as likely to have UTUC as patients with invasive disease [612]. Multifocality increases the risk of recurrence by three-fold, while positive ureteral or urethral margins increase the risk by seven-fold. Radical nephroureterectomy can prolong survival [613].

8.3 Time schedule for surveillance

Although, based on low level evidence only, some follow-up schedules have been suggested, guided by the principle that recurrences tend to occur within the first years following initial treatment. A schedule suggested by the EAU Guidelines Panel includes a CT scan (every 6 months) until the third year, followed by annual imaging thereafter. Patients with multifocal disease, NMIBC with CIS or positive ureteral margins are at higher risk of developing UTUC, which can develop late (> 3 years). In those cases, monitoring of the UUT is mandatory during follow-up. Computed tomography is to be used for imaging of the UUT [612].

The exact time to stop follow-up is not well known and recently a risk-adapted schedule has been proposed, based on the interaction between recurrence risk and competing health factors that could lead to individualised recommendations and may increase recurrence detection. Elderly and very low-risk patients (those with NMIBC or pT0 disease at final cystectomy report) showed a higher competing risk of non-BC mortality when compared with their level of BC recurrence risk. On the other hand, patients with locally-advanced disease or LN involvement are at a higher risk of recurrence for more than 20 years [614]. However, this model has not been validated, does not differentiate between pure UC or variant histologies, and does not incorporate several risk factors related to non-BC mortality. Variant histology tumours (including urothelial variants,

non-urothelial variants, and mixed variants) might be associated with a greater recurrence risk than PUC. Recently, a different follow-up scheme for patients with variant histology tumours has been proposed [615]. In case of pT0 patients with previous variant histology in TURB or in those in the age range between 60 and 79 years, the follow-up should be longer than in PUC since the risk of recurrence persists over time. Similar to PUC, patients older than 80 years with variant histology tumours might not need oncologic surveillance given the higher risk of non-BC mortality compared to the risk of recurrence whereas patients younger than 60 years should be offered extended surveillance (> 10 years) since the risk of recurrence will exceed that of non-BC mortality [615]. Future prospective studies are needed to answer the question whether a more intense follow-up for variant histologies should be considered.

Furthermore, the prognostic implications of the different sites of recurrence should be considered. Local and systemic recurrences have a poor prognosis and early detection of the disease will not influence survival [616]. Despite this, the rationale for a risk-adapted schedule for BC surveillance appears to be promising and deserves further investigation.

Since data for follow-up strategies are sparse, a number of key questions were included in a recently held consensus project [8, 9]. Outcomes for all statements for which consensus was achieved are listed in Section 8.6.

8.4 Follow-up of functional outcomes and complications

Apart from oncological surveillance, patients with a urinary diversion need functional follow-up. Complications related to urinary diversion are detected in 45% of patients during the first five years of follow-up. This rate increases over time, and exceeds 54% after 15 years of follow-up. In a single-centre series of 259 male patients, long-term follow-up after orthotopic bladder substitution (median 121 months [range 60–267]), showed that excellent long-term functional outcomes can be achieved in high-volume centres with dedicated teams [617]. A smaller multi-centre series including women only (n = 102) showed complication rates between 5–12% after orthotopic neobladder (median follow-up of 24 months [range 1.5–100 months]). Both early (5%) and late (12%) complications related to the urinary diversion [618].

The functional complications are diverse and include: vitamin B12 deficiency, metabolic acidosis, worsening of renal function, urinary infections, urolithiasis, ureteroenteric stricture [619], stoma complications in patients with ileal conduit, neobladder continence problems, and emptying dysfunction [600]. Benign ureteroenteric strictures may occur in up to 20% of patients [619]. Functional complications are especially common in women: approximately two-thirds need to catheterise their neobladder, while almost 45% do not void spontaneously at all [586]. There seems to be a correlation between voiding patterns and nerve preservation; in 66 women bilateral preservation of autonomic nerves decreased the need for catheterisation to between 3.4–18.7% (CI: 95%) [618].

Based on SEER data, cystectomy was found to be associated with a 21% increased risk of fractures compared to no RC due to chronic metabolic acidosis and subsequent long-term bone loss [616].

Since low vitamin B12 levels have been reported in 17% of patients with bowel diversion, in case of cystectomy and bowel diversion, vitamin B12 levels should be measured annually [8, 9, 411].

8.5 Summary of evidence and recommendations for specific recurrence sites

Site of recurrence	Summary of evidence	Recommendation	Strength rating
Local recurrence	Poor prognosis. Treatment should be individualised depending on the local extent of tumour.	Offer radiotherapy, chemotherapy and possibly surgery as options for treatment, either alone or in combination.	Strong
Distant recurrence	Poor prognosis.	Offer chemotherapy as the first option, and consider metastasectomy or radiotherapy in case of unique metastasis site.	Strong
Upper urinary tract recurrence	Risk factors are multifocal disease, NMIBC/CIS or positive ureteral margins.	See EAU Guidelines on Upper Urinary Tract Urothelial Carcinomas.	Strong
Secondary urethral tumour	Staging and treatment should be done as for primary urethral tumour.	See EAU Guidelines on Primary Urethral Carcinoma.	Strong

8.6 EAU-ESMO consensus statements on the management of advanced- and variant bladder cancer [8, 9]*

Consensus statement
After radical cystectomy with curative intent, regular follow-up is needed.
After radical cystectomy with curative intent, follow-up for the detection of second cancers in the urothelium is recommended.
After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g., multifocality, carcinoma *in situ* and tumour in the prostatic urethra).
After trimodality treatment with curative intent, follow-up for the detection of relapse is recommended every 3–4 months initially; then after 3 years, every 6 months in the majority of patients.
After trimodality treatment with curative intent, regular follow-up for the detection of relapse is needed in the majority of patients.
After trimodality treatment with curative intent, follow-up imaging to assess distant recurrence or recurrence outside the bladder is needed.
After trimodality treatment with curative intent, assessment of the urothelium to detect recurrence is recommended every 6 months in the majority of patients.
After trimodality treatment with curative intent, in addition to a CT scan, other investigations of the bladder are recommended.
In patients with a partial or complete response after chemotherapy for metastatic urothelial cancer, regular follow-up is needed. Imaging studies may be done according to signs/symptoms.
To detect relapse (outside the bladder) after trimodality treatment with curative intent, CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.
To detect relapse (outside the bladder) after trimodality treatment with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 years in the majority of patients.
In patients treated with radical cystectomy with curative intent and who have a neobladder, management of acid bases household includes regular measurements of pH and sodium bicarbonate substitution according to the measured value.
To detect relapse after radical cystectomy with curative intent, routine imaging with CT of the thorax and abdomen should be stopped after 5 years in the majority of patients.
To detect relapse after radical cystectomy with curative intent, a CT of the thorax and abdomen is recommended as the imaging method for follow-up in the majority of patients.
Levels of LDH and CEA are not essential in the follow-up of patients with urothelial cancer to detect recurrence.
Vitamin B12 levels have to be measured annually in the follow-up of patients treated with radical cystectomy and bowel diversion with curative intent.

**Only statements which met the a priori consensus threshold across all three stakeholder groups are listed (defined as ≥ 70% agreement and ≤ 15% disagreement, or vice versa).*
CEA = carcinoembryonic antigen; CT = computed tomography; LDH = lactate dehydrogenase.

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Working Group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guideline/bladder-cancer-muscle-invasive-and-metastatic/?type=panel.

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11. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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EAU Guidelines on

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Neuro-Urology Guidelines aim to provide information for clinical practitioners on the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. These Guidelines reflect the current opinion of experts in this specific pathology and represent a state-of-the-art reference for all clinicians, as of the publication date.

The terminology used and the diagnostic procedures advised throughout these Guidelines follow the recommendations for investigations of the lower urinary tract (LUT) as published by the International Continence Society (ICS) [1-3]. Readers are advised to consult other EAU Guidelines that may address different aspects of the topics discussed in this document.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Neuro-Urology Guidelines Panel consists of an international multidisciplinary group of neuro-urological experts. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/neuro-urology/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation with the full text version. A guideline summary has also been published in European Urology [4]. All are available through the EAU website: http://www.uroweb.org/guideline/neurourology/.

1.4 Publication history

The EAU published the first Neuro-Urology Guidelines in 2003 with updates in 2008, 2014, 2017, 2019. This 2022 document represents a limited update of the 2020 publication. The literature was assessed for all chapters.

1.5 Background

The function of the LUT is mainly storage and voiding of urine, which is regulated by the nervous system that coordinates the activity of the urinary bladder and bladder outlet. The part of the nervous system that regulates LUT function is disseminated from the peripheral nerves in the pelvis to highly specialised cortical areas. Any disturbance of the nervous system involved, can result in neuro-urological symptoms. The extent and location of the disturbance will determine the type of LUT dysfunction, which can be symptomatic or asymptomatic. Neuro-urological symptoms can cause a variety of long-term complications; the most significant being deterioration of renal function. Since symptoms and long-term complications do not correlate [5], it is important to identify patients with neuro-urological symptoms, and establish if they have a low or high risk of subsequent complications. The risk of developing upper urinary tract (UUT) damage and renal failure is much lower in patients with slowly progressive non-traumatic neurological disorders than in those with spinal cord injury or spina bifida [6]. In summary, treatment and intensity of follow-up examinations are based on the type of neuro-urological disorder and the underlying cause.

2. METHODS

2.1 Introduction

For the 2022 Neuro-Urology Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Neuro-Urology Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between the 1st of May 2019 and 1st May 2021. A total of 1,743 unique records were identified, retrieved, and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/neuro-urology/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [7, 8]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [9];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [10]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

Publications ensuing from panel-lead systematic reviews (SR) have all been peer-reviewed. The 2015 Neuro-Urology Guidelines were subject to peer review prior to publication.

3. THE GUIDELINE

3.1 Epidemiology, aetiology and pathophysiology

*3.1.1 **Introduction***

Neuro-urological symptoms may be caused by a variety of diseases and events affecting the nervous system controlling the LUT. The resulting neuro-urological symptoms depend predominantly on the location and the extent of the neurological lesion. There are no exact figures on the overall prevalence of neuro-urological disorders in the general population, but data are available on the prevalence of the underlying conditions and the relative risk of these for the development of neuro-urological symptoms. It is important to note that the majority of the data shows a very wide range of prevalence/incidence. This reflects the variability in the cohort (e.g., early or late-stage disease) and the frequently small sample sizes, resulting in a low level of evidence in most published data (summarised in Table 1).

Table 1: Epidemiology of Neuro-Urological Disorders

Suprapontine and pontine lesions and diseases		
Neurological Disease	**Frequency in General Population**	**Type and Frequency of Neuro-Urological Symptoms**
Cerebrovascular accident (Strokes)	450 cases/100,000/yr (Europe) [11], 10% of cardiovascular mortality.	Nocturia - overactive bladder (OAB) - urgency urinary incontinence (UUI) - detrusor overactivity (DO), other patterns less frequent [12]. 57-83% of neuro-urological symptoms at one month post-stroke, 71-80% spontaneous recovery at six months [13]. Persistence of urinary incontinence (UI) correlates with poor prognosis [14].
Dementias: Alzheimer's disease (80%), Vascular (10%), Other (10%).	6.4% of adults > 65 yrs [15].	OAB - UUI – DO, 25% of incontinence in Alzheimer's disease, > 25% in other dementias: Lewy body, NPH, Binswanger, Nasu-Hakola, Pick Disease [16]. Incontinence three times more frequent in geriatric patients with dementia than without [17].
Parkinsonian syndrome (PS) Idiopathic Parkinson's disease (IPD): 75-80% of PS. Non-IPD: Parkinson's-plus (18%): - Multiple system atrophy (MSA), - Progressive supranuclear palsy, - Corticobasal degeneration, - Dementia with Lewy bodies. Secondary Parkinson's (2%).	Second most prevalent neurodegenerative disease after Alzheimer's disease. Rising prevalence of IPD with age [18]. MSA is the most frequent non-IPD PS.	Urinary symptoms affect 50% at onset, with urgency and nocturia being the most common. Patients with urinary symptoms at presentation have worse disease progression in Parkinson's disease [19]. Infections account for a major cause of mortality in MSA [20]. Impaired detrusor contractility with post-void residual (PVR) > 150 mL seems to be the urodynamic finding distinguishing MSA from IPD [21-23].
Brain tumours	26.8/100,000/yr in adults (> 19 yrs), (17.9 benign, 8.9 malignant) [24].	Incontinence occurs mainly in frontal location (part of frontal syndrome or isolated in frontal location) [25].
Cerebral palsy	Cerebral palsy: 3.1-3.6/1,000 in children aged 8 yrs [26].	46% of patients with cerebral palsy suffer from UI, with 85% of patients having abnormal urodynamic studies (Neurogenic DO most common 59%). Upper tract deterioration is rare (2.5%) [27].
Traumatic brain injury	235/100,000/yr [28].	44% storage dysfunction, 38% voiding dysfunction, 60% urodynamic abnormalities [29].
Normal pressure hydrocephalus	0.5% of the population > 60, up to 2.9% of those > 65 [30].	Classic triad of gait and cognitive disturbance along with UI. Incontinence affects 98-100% of patients [30].
Lesions and diseases between caudal brainstem and sacral spinal cord		
Spinal cord injury (SCI)	Prevalence of traumatic SCI in developed countries ranges from 280 to 906/million [31].	Neurogenic DO and detrusor sphincter dyssynergia (DSD) (up to 95%) and detrusor underactivity (DU) (up to 83%) depending on the level of the lesion [32].

Spina bifida (SB)	Spina bifida 3-4/10,000 Lumbar and lumbosacral form are the most common (60%) [33].	Bladder function is impaired in up to 96% of SB patients [34]. Over 50% of patients are incontinent [35]. Patients with open and closed defects can have equally severe neurogenic LUT dysfunction [36].
Hereditary spastic paraplegia (HSP)	Prevalence 1.3-9/100,000 [37].	LUTS in about 75%, mainly urgency and voiding dysfunction. Neurogenic DO in 81% (of whom 76% with DSD) [37].
Lesions and diseases of the peripheral nervous system		
Lumbar spine Degenerative disease Disk prolapse Lumbar canal stenosis	Male (5%) and female (3%) > 35 yr have had a lumbosciatic episode related to disc prolapse. Incidence: approx. 5/100,000/yr More common in females > 45 yr.	26% difficulty to void and acontractile detrusor [38]. Detrusor underactivity (up to 83%) [32]. Tarlov cysts: early sensation of filling (70%), NDO (33%), urethral instability (33%) and stress urinary incontinence (SUI) (33%) [39].
Iatrogenic pelvic nerve lesions	Rectal cancer. Cervical cancer (multimodal therapy, radiotherapy and surgery). Endometriosis surgery.	After abdomino-perineal resection: 50% urinary retention. After total mesorectal excision: 10-30% voiding dysfunction [40].
Peripheral neuropathy Diabetes Other causes of peripheral neuropathy causing neuro-urological symptoms: alcohol abuse; lumbosacral zona and genital herpes; Guillain Barré syndrome; porphyria and sarcoidosis.	Worldwide, prevalence of pharmacologically treated diabetes 8.3% [41].	Urgency/frequency +/- incontinence [42]. Hyposensitive and detrusor underactivity at later phase [42].
Disseminated central diseases		
Multiple sclerosis (MS)	Prevalence: 83/100,000 in Europe [43].	10% of MS patients present with voiding dysfunction at disease onset, 75% of patients will develop it after 10 yrs of MS [44]. DO: 65% [44], 43% [45]. DSD: 35% [44, 45]. Detrusor underactivity: 25% [44].

3.2 Classification systems

3.2.1 Introduction

Relevant definitions can be found in the general ICS standardisation reports [2, 3, 46]. Supplementary online Tables S1 and S2 list the definitions from these references, partly adapted, and other definitions considered useful for clinical practice: https://uroweb.org/guideline/neuro-urology/?type=appendices-publications.

3.3 Diagnostic evaluation

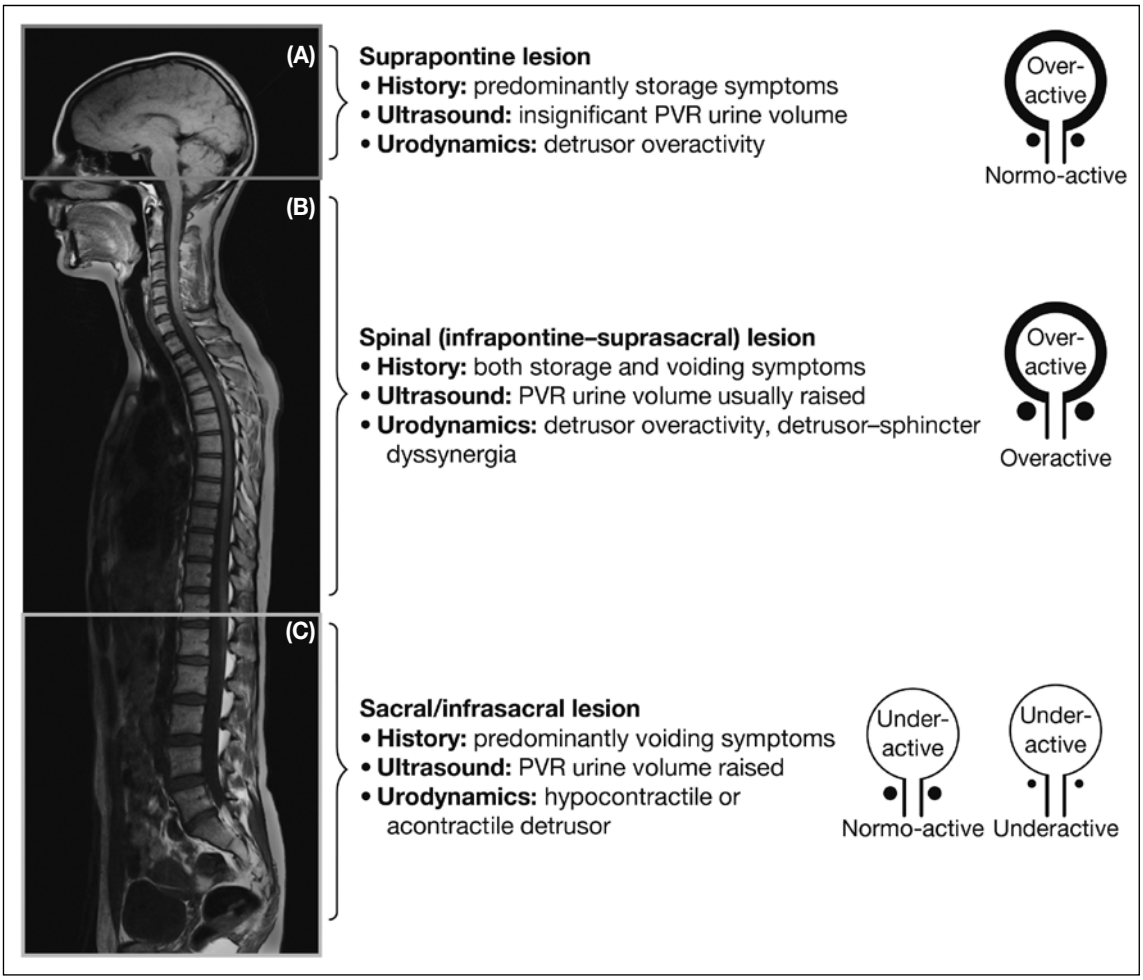
3.3.1 Introduction

The normal physiological function of the LUT depends on an intricate interplay between the sensory and motor nervous systems. When diagnosing neuro-urological symptoms, the aim is to describe the type of dysfunction involved. A thorough medical history, physical examination and bladder diary are mandatory before any additional diagnostic investigations can be planned. Results of the initial evaluation are used to decide the patient's long-term treatment and follow-up.

3.3.2 Classification systems

The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. A very simple classification system for use in daily clinical practice to decide on the appropriate therapeutic approach is provided in Figure 1 [6].

Figure 1: Patterns of lower urinary tract dysfunction following neurological disease



The pattern of LUT dysfunction following neurological disease is determined by the site and nature of the lesion. Panel (A) denotes the region above the pons, panel (B) the region between the pons and the sacral cord and panel (C) the sacral cord and infrasacral region. Figures on the right show the expected dysfunctional states of the detrusor-sphincter system. Figure adapted from Panicker et al., [6] with permission from Elsevier.
PVR = post-void residual.

3.3.3 Timing of diagnosis and treatment

Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders. This helps to prevent irreversible changes within the LUT, even in the presence of normal reflexes [47]. Furthermore, urological symptoms can be the presenting feature of neurological pathology [48, 49]. Early intervention can prevent irreversible deterioration of the LUT and UUT [49]. Long term follow-up (life-long) is mandatory to assess risk of UUT damage and renal failure [50].

3.3.4 Patient history

History taking should include past and present symptoms and disorders (Table 4). It is the cornerstone of evaluation, as the answers will aid selection of diagnostic investigations and treatment options.

- In non-traumatic neuro-urological patients with an insidious onset, a detailed history may find that the condition started in childhood or adolescence [51].
- Urinary history consists of symptoms associated with both urine storage and voiding.
- Bowel history is important because patients with neuro-urological symptoms may also have related neurogenic bowel dysfunction [52].
- Sexual function may be impaired because of the neuro-urological condition [53].
- Special attention should be paid to possible warning signs and symptoms (e.g., pain, infection, haematuria, and fever) requiring further investigation.
- Patients with SCI usually find it difficult to report urinary tract infection (UTI)-related symptoms accurately [54, 55].

- The presence of urinary, bowel and sexual symptoms without neurological symptoms could be suggestive of an underlying neurological disease or condition.
- The severity of lesion after acute SCI does not predict the presence or absence of unfavourable urodynamic parameters [47].

Table 4: History taking in patients with suspected neuro-urological disorder

Past history
Childhood through to adolescence and into adulthood
Hereditary or familial risk factors
Specific female: menarche (age); this may suggest a metabolic disorder
Obstetric history
History of diabetes
Diseases, e.g., multiple sclerosis, parkinsonism, encephalitis, syphilis
Accidents and operations, especially those involving the spine and central nervous system
Present history
Present medication
Lifestyle (smoking, alcohol and drugs); may influence urinary, sexual and bowel function
Quality of life
Specific urinary history
Onset of urological history
Relief after voiding; to detect the extent of a neurological lesion in the absence of obstructive uropathy
Bladder sensation (painful, abnormal, absent or increased)
Initiation of micturition (normal, precipitate, reflex, strain, Credé)
Interruption of micturition (normal, paradoxical, passive)
Enuresis
Mode and type of voiding (catheterisation)
Frequency, voided volume, incontinence, urgency episodes
Sexual history
Genital or sexual dysfunction symptoms
Sensation in genital area (absent, increased, abnormal, pain)
Specific male: libido, erection, (lack of) orgasm, ejaculation
Specific female: libido, dyspareunia, (lack of) orgasm
Bowel history
Frequency and faecal incontinence
Desire to defecate
Defecation pattern
Rectal sensation
Initiation of defecation (digital stimulation, enema, suppositories)
Neurological history
Acquired or congenital neurological condition
Mental status and comprehension
Neurological symptoms (somatic and sensory), with onset, evolution, and any treatment
Spasticity or autonomic dysreflexia (AD) (especially in lesions at or above level Th 6)
Mobility and hand function

3.3.4.1 Bladder diaries

Bladder diaries are considered a valuable diagnostic tool for the initial assessment of neurogenic LUT dysfunction. They provide data on the number of voids (spontaneous or intermittent catheter), voided volume, UUI episodes and contribute to the interpretation of urodynamic testing. Preferably, bladder diaries should be completed for three consecutive days [56].

*3.3.5 **Patient quality of life questionnaires***

An assessment of the patient's present and expected future quality of life (QoL) is important to evaluate the effect of any therapy. Quality of life is an essential aspect of the overall management of neuro-urological patients, for example when evaluating treatment related changes on a patient's QoL [57]. The type of bladder management has been shown to affect health-related QoL (HRQoL) mainly in patients with SCI [58, 59] and MS

[60], as does the presence or absence of urinary, sexual and faecal incontinence [61]. Other research has also highlighted the importance of urological treatment and its impact on the urodynamic functionality of the neuro-urological patient in determining patient QoL [62].

In recent years a proliferation in the number of questionnaires to evaluate symptoms and QoL has been seen. Condition-specific questionnaires can be used to assess symptom severity and the impact of symptoms on QoL. A patient's overall QoL can be assessed using generic questionnaires. It is important that the questionnaire of choice has been validated in the neuro-urological population, and that it is available in the language that it is to be used in.

3.3.5.1 Available Questionnaires

Three condition-specific questionnaires for urinary or bowel dysfunction and QoL have been developed specifically for adult neuro-urological patients [63]. In MS and SCI patients the Qualiveen, also available in a short version, is validated and translated into various languages [64, 65]. Although several objective and subjective tools have been used to assess the influence of neurogenic lower urinary tract dysfunctions (N-LUTD) on QoL in SCI, the Quality life index-SCI and Qualiveen are the only validated condition-specific outcomes that have shown consistent sensitivity [66]. The Neurogenic Bladder Symptom Score (NBSS) and its short version has been validated in neurological patients to measure urinary symptoms and their consequences [67-69]. The QoL scoring tool related to Bowel Management (QoL-BM) [70] can be used to assess bowel dysfunction in MS and SCI patients. A new tool has recently been developed to understand the reasons for poor compliance in long-term management of neurogenic patients. [71, 72]. A variety of patient-reported outcome measures (PROMs) are available to evaluate sexual function in neuro-urological patients. However, only the Multiple Sclerosis Intimacy and Sexuality Questionnaire-15 (MSISQ-15) and -19 is supported by evidence [73-75].

In addition, several validated questionnaires that evaluate QoL and assess urinary symptoms as a subscale or question in neuro-urological patients have been identified [76] (Table 5). The condition-specific Incontinence-Quality of Life (I-QoL) questionnaire which was initially developed for the non-neurological population has now also been validated for neuro-urological patients [77].

A patient's overall QoL can be assessed by generic HRQoL questionnaires, the most commonly used being the I-QOL, King's Health Questionnaire (KHQ), or the Short Form 36-item and 12-item Health Survey Questionnaires (SF-36, SF-12) [63]. In addition, the quality-adjusted life year (QALY), quantifies outcomes, by weighing years of life spent in a specified health state, adjusted by a factor representing the value placed by society or patients on their specific health state [78].

No evidence was found for which validated questionnaires are the most appropriate for use, since no quality criteria for validated questionnaires have been assessed [63].

Table 5: Patient questionnaires

Questionnaire	Underlying neurological disorder	Bladder	Bowel	Sexual function
FAMS [79]	MS	X		X
FILMS [80]	MS	X	X	
HAQUAMS [81]	MS	X	X	X
I-QOL [77]	MS, SCI	X		X
LUTS-TCA [71]	MS, SCI, Parkinson	X		
MDS [82]	MS	X	X	
MSISQ-15 / MSISQ-19 [73, 74]	MS, SCI	X	X	X
MSQLI [83]	MS	X	X	X
MSQoL-54 [84]	MS	X	X	X
MSWDQ [85]	MS	X	X	
NBSS [67, 69]	MS, SCI, SB, Cerebral Palsy	X		
NBSS-SF [68]	MS, SCI, SB			
QoL-BM [70]	SCI		X	
Qualiveen/SF-Qualiveen [65, 86]	MS, SCI	X		X
RAYS [87]	MS	X		X
RHSCIR [88]	SCI	X	X	X
USQNB [72]	SCI	X	X	

3.3.6 ***Physical examination and additional tests***

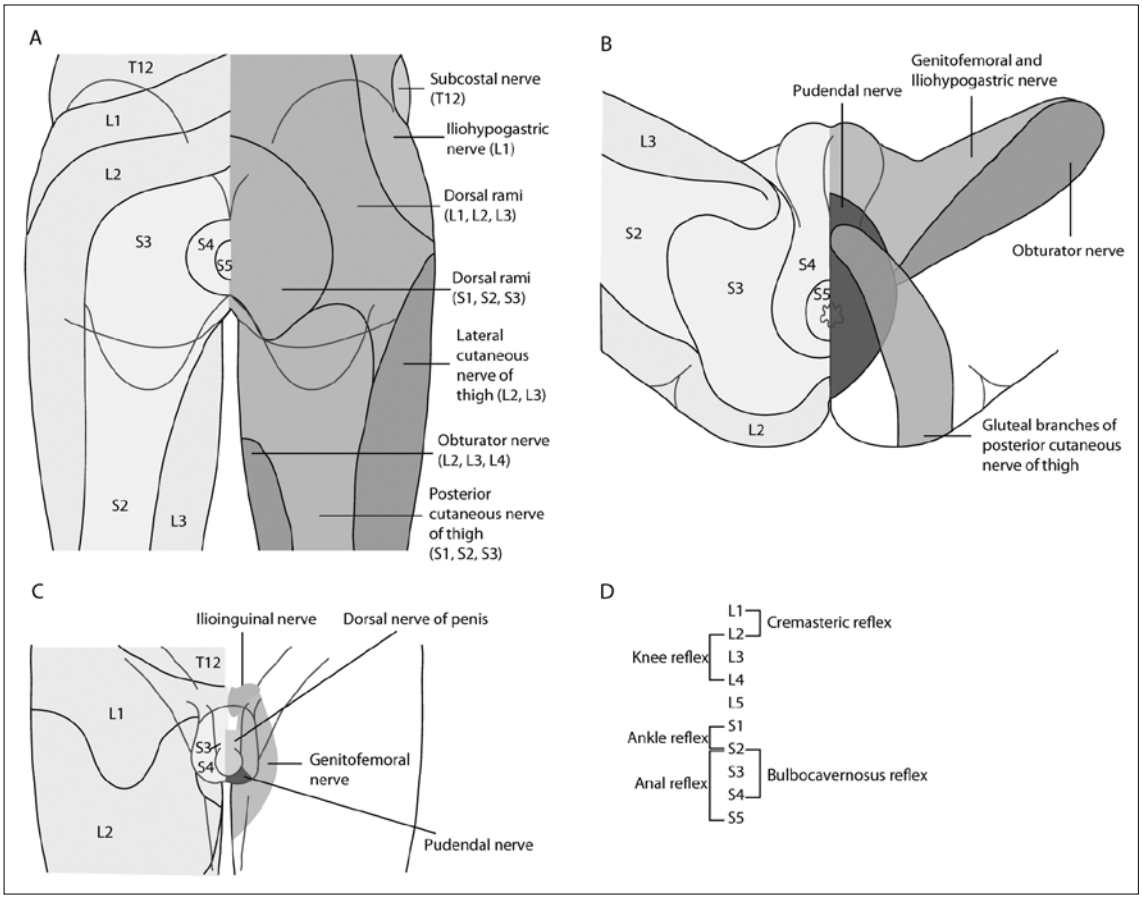
In addition to a detailed patient history, attention should be paid to possible physical and intellectual disabilities with respect to the planned investigations [89, 90]. Neuro-urological status should be described as completely as possible (Figure 2) [6]. Patients with a high spinal cord lesion or supraspinal neurological lesions may suffer from a significant drop in blood pressure when moved into a sitting or standing position. All sensations and reflexes in the urogenital area must be tested [6]. Furthermore, detailed testing of the anal sphincter and pelvic floor functions must be performed (Figure 2) [6, 91]. It is essential to have this clinical information to reliably interpret later diagnostic investigations (Table 6).

Additionally, urinalysis, blood chemistry, ultrasonography, post void residual, incontinence quantification and were indicated free uroflowmetry, should be performed as part of the routine assessment of neuro-urological patients [6, 92].

3.3.6.1 *Autonomic dysreflexia*

Autonomic dysreflexia is a sudden and exaggerated autonomic response to various stimuli generally manifests in patients with SCI or spinal dysfunction at or above level Th 6. It is defined by an increase in systolic blood pressure > 20 mmHg from baseline [93] and can have life-threatening consequences if not managed adequately. The stimulus can be distended bladder or bowel. For example, iatrogenic stimuli during cystoscopy or urodynamics can trigger AD [94]. It can also be secondary to sexual stimulation or any noxious stimulus, e.g., infected toenail or pressure sore.

Figure 2: Lumbosacral dermatomes, cutaneous nerves, and reflexes



The physical examination includes testing sensations and reflexes mediated through the lower spinal cord. Abnormal findings would suggest a lesion affecting the lumbosacral segments; mapping out distinct areas of sensory impairment helps to further localise the site of the lesion. Distribution of dermatomes (areas of skin mainly supplied by a single spinal nerve) and cutaneous nerves over the perianal region and back of the upper thigh (A), the perineum [95] (B), male external genitalia [96] (C) and root values of lower spinal cord reflexes (D). Figure adapted from Panicker et al., [6] with parts A-C adapted from Standring [97], both with permission from Elsevier.

Table 6: Neuro-urological items to be specified

Sensation S2-S5 (both sides)
Presence (increased/normal/reduced/absent)
Type (light touch/pin prick)
Affected dermatomes
Reflexes (increased/normal/reduced/absent)
Bulbocavernous reflex
Perianal/anal reflex
Knee and ankle reflexes
Plantar responses (Babinski)
Anal sphincter tone
Presence (increased/normal/reduced/absent)
Voluntary contractions of anal sphincter and pelvic muscles (increased/normal/reduced/absent)
General urogenital assessment
Prostate palpation
Skin lesions
Size and presence of penis
Descensus (prolapse) of pelvic organs

3.3.6.2 Summary of evidence and recommendations for history taking and physical examination

Summary of evidence	**LE**
Early diagnosis and treatment are essential in both congenital and acquired neuro-urological disorders to prevent irreversible changes within the LUT.	4
An extensive general history is the basis of evaluation focusing on past and present symptoms including urinary, sexual, bowel and neurological function.	4
Assessment of present and expected future QoL is an essential aspect of the overall management of neuro-urological patients and is important to evaluate the effect of any therapy.	2a
Quality of life assessment should be completed with validated QoL questionnaires for neuro-urological patients.	1a
Bladder diaries provide data on the number of voids, voided volume, urinary incontinence, and urgency episodes.	3

Recommendations	**Strength rating**
History taking	
Take an extensive general history, concentrating on past and present symptoms.	Strong
Take a specific history for each of the four mentioned functions - urinary, bowel, sexual and neurological.	Strong
Pay special attention to the possible existence of alarm signs (e.g. pain, infection, haematuria, fever) that warrant further specific diagnosis.	Strong
Assess quality of life when evaluating and treating neuro-urological patients.	Strong
Use available validated tools for urinary and bowel symptoms in neuro-urological patients.	Strong
Use MSISQ-15 or MSISQ-19 to evaluate sexual function in multiple sclerosis patients.	Strong
Physical examination	
Acknowledge individual patient disabilities when planning further investigations.	Strong
Describe the neurological status as completely as possible, sensations and reflexes in the urogenital area must all be tested.	Strong
Test the anal sphincter and pelvic floor functions.	Strong
Perform urinalysis, blood chemistry, bladder diary, post-void residual, incontinence quantification and urinary tract imaging as initial and routinary evaluation.	Strong

MSISQ 15/19 = Multiple Sclerosis Intimacy and Sexuality Questionnaire 15/19 question version.

3.3.7 ***Urodynamics***

3.3.7.1 Introduction

Urodynamic investigation is the only method that can objectively assess the function and dysfunction of the LUT. In neuro-urological patients, invasive urodynamic investigation is even more challenging than in general patients. Any technical source of artefacts must be critically considered. It is essential to maintain the quality of the urodynamic recording and its interpretation [1]. Same session repeat urodynamic investigations are crucial in clinical decision making, since repeat measurements may yield completely different results [98].

In patients at risk of AD, it is advisable to measure blood pressure during the urodynamic study [99, 100]. The rectal ampulla should be empty of stool before the start of the investigation. All urodynamic findings must be reported in detail and performed, according to the ICS technical recommendations and standards [1, 101].

3.3.7.2 Urodynamic tests

Free uroflowmetry and assessment of residual urine: It is recommended prior to planning any invasive urodynamics that patients are able to void in the usual position. For reliable information, it should be repeated at least two to three times [1]. Possible pathological findings include a low flow rate, low voided volume, intermittent flow, hesitancy and PVR.

Filling cystometry: This test is the only method for quantifying the patient's filling function. The status of LUT function must be documented during the filling phase. However, this technique has limited use as a solitary procedure. It is much more effective combined with bladder pressure measurement during micturition and is even more effective in video-urodynamics.

The bladder should be empty at the start of filling. A physiological filling rate should be used with body-warm saline. Possible pathological findings include neurogenic detrusor overactivity (NDO), low bladder compliance, abnormal bladder sensations, low cystometric capacity and urinary incontinence.

Detrusor leak point pressure [112]: Appears to have no use as a diagnostic tool. Some positive findings have been reported [50, 103, 104], but sensitivity is too low to estimate the risk to the UUT or for secondary bladder damage [105, 106].

Pressure flow study (or voiding cystometry): Reflects the coordination between detrusor and urethra or pelvic floor during the voiding phase. It is even more effective if combined with filling cystometry and video-urodynamics. Possible pathological findings include detrusor underactivity, acontractility, bladder outlet obstruction (BOO), DSD, a high urethral resistance, and residual urine.

Most types of obstruction caused by neuro-urological disorders are due to DSD [107, 108], non-relaxing urethra, and/or non-relaxing bladder neck [109, 110]. Pressure-flow analysis mainly assesses the amount of mechanical obstruction caused by the urethra's inherent mechanical and anatomical properties and has limited value in patients with neuro-urological disorders.

Electromyography (EMG): Reflects the activity of the external urethral sphincter, the peri-urethral striated musculature, the anal sphincter, and the striated pelvic floor muscles. Correct interpretation may be difficult due to artefacts introduced by other equipment. In the urodynamic setting, an EMG is useful as a gross indication of the patient's ability to control the pelvic floor. Possible pathological findings include inadequate recruitment upon specific stimuli (e.g. bladder filling, involuntary detrusor contractions, onset of voiding, coughing, Valsalva manoeuvre) suggesting a diagnosis of DSD [111].

Urethral pressure measurement: Has a very limited role in neuro-urological disorders. There is no consensus on parameters indicating pathological findings [112].

Video-urodynamics: Is the combination of filling cystometry and pressure flow studies with imaging. It is the optimum procedure for urodynamic investigation in neuro-urological disorders [5]. Possible pathological findings include all those described in the filling cystometry and the pressure flow study sections, and any morphological pathology of the LUT and reflux to the UUT [113].

Ambulatory urodynamics: This is the functional investigation of the urinary tract, which predominantly uses the natural filling of the urinary tract to reproduce the patient's normal activity. Although this type of study might be considered when conventional urodynamics does not reproduce the patient's symptoms, its role in the neuro-urological patient still needs to be determined [114, 115].

Triggered tests during urodynamics: Lower urinary tract function can be provoked by coughing, triggered voiding, or anal stretch. Fast-filling cystometry with cooled saline (the 'ice water test') was initially described to discriminate between upper and lower motor neuron lesions [116, 117]. Patients with upper motor neuron lesions develop a detrusor contraction if the detrusor is intact, while patients with lower motor neuron lesions do not. However, the test does not seem to be fully discriminative since also non neurological and lower motor SCI have shown positive test [118, 119].

Previously, a positive bethanechol test [120] (detrusor contraction > 25 cm H_2O) was thought to indicate detrusor denervation hypersensitivity and the muscular integrity of an acontractile detrusor. However, in practice, the test has given equivocal results. A variation of this method was reported using intravesical electromotive administration of the bethanechol [121], but there was no published follow-up. Currently, there is no indication for this test.

3.3.7.3 Specialist uro-neurophysiological tests

The following tests are advised as part of the neurological work-up [122]:

- electromyography (in a neurophysiological setting) of pelvic floor muscles, urethral sphincter and/or anal sphincter;
- nerve conduction studies of pudendal nerve;
- reflex latency measurements of bulbocavernosus and anal reflex arcs;
- evoked responses from clitoris or glans penis;
- sensory testing on bladder and urethra.

Other elective tests, for specific conditions, may become obvious during the work-up and urodynamic investigations.

3.3.7.4 Summary of evidence and recommendations for urodynamics and uro-neurophysiological tests

Summary of evidence	**LE**
Urodynamic investigation is the only method that can objectively assess the (dys-)function of the LUT.	2a
Video-urodynamics is the optimum procedure for urodynamic investigation in neuro-urological disorders.	4
Specific uro-neurophysiological tests are elective procedures and should only be carried out in specialised settings.	4

Recommendations	**Strength rating**
Perform a urodynamic investigation to detect and specify lower urinary tract (dys-)function, use same session repeat measurement as it is crucial in clinical decision making.	Strong
Non-invasive testing is mandatory before invasive urodynamics is planned.	Strong
Use video-urodynamics for invasive urodynamics in neuro-urological patients. If this is not available, then perform a filling cystometry continuing into a pressure flow study.	Strong
Use a physiological filling rate and body-warm saline.	Strong

3.3.8 ***Renal function***

In many patients with neuro-urological disorders, the UUT is at risk, particularly in patients who develop high detrusor pressure during the filling phase. Although effective treatment can reduce this risk, there is still a relatively high incidence of renal morbidity [123, 124]. Patients with SCI or SB have a higher risk of developing renal failure compared with patients with slowly progressive non-traumatic neurological disorders, such as MS and Parkinson's disease (PD) [125].

Caregivers must be informed of this risk and instructed to watch carefully for any signs or symptoms of a possible deterioration in the patient's renal function. In patients with poor muscle mass cystatin C based glomerular filtration rate (GFR) is more accurate in detecting chronic kidney disease than serum creatinine estimated GFR [126, 127]. There are no high-level evidence publications available which show the optimal management to preserve renal function in these patients [128].

3.4 Disease management

*3.4.1 **Introduction***

The primary aims for treatment of neuro-urological symptoms, and their priorities, are [129, 130]:

- protection of the UUT;
- achievement (or maintenance) of urinary continence;
- restoration of LUT function;
- improvement of the patient's QoL.

Further considerations are the patient's disability, cost-effectiveness, technical complexity and possible complications [130].

Renal failure is the main mortality factor in SCI patients who survive the trauma [131, 132]. Keeping the detrusor pressure during both the filling and voiding phases within safe limits significantly reduces the mortality from urological causes in these patients [133-135] and has consequently become the top priority in the treatment of patients with neuro-urological symptoms [129, 130].

In patients with high detrusor pressure during the filling phase (DO, low bladder compliance), treatment is aimed primarily at conversion of an overactive, high-pressure bladder into a low-pressure reservoir despite the resulting residual urine [129]. Reduction of the detrusor pressure contributes to urinary continence, and consequently to social rehabilitation and QoL. It is also critical for preventing UTIs [136, 137]. However, complete continence cannot always be obtained.

*3.4.2 **Non-invasive conservative treatment***

3.4.2.1 Assisted bladder emptying - Credé manoeuvre, Valsalva manoeuvre, triggered reflex voiding

Incomplete bladder emptying is a serious risk factor for UTI, high intravesical pressure and incontinence. Methods to improve the voiding process should therefore be practiced.

Bladder expression: The downwards movement of the lower abdomen by suprapubic compression (Credé) or by abdominal straining (Valsalva) leads to an increase in intravesical pressure, and generally also causes a reflex sphincter contraction [138, 139]. The latter may increase bladder outlet resistance and lead to inefficient emptying. The high pressures created during these procedures are hazardous for the urinary tract [140, 141]. Therefore, their use should be discouraged unless urodynamics show that the intravesical pressure remains within safe limits [130].

Long-term complications are unavoidable for both methods of bladder emptying [139]. The already weak pelvic floor function may be further impaired, thus introducing or exacerbating already existing SUI [141].

Triggered reflex voiding: Stimulation of the sacral or lumbar dermatomes in patients with a upper motor neuron lesion can elicit a reflex detrusor contraction [141]. The risk of high pressure voiding is present and interventions to decrease outlet resistance may be necessary [142]. Triggering can induce AD, especially in patients with high level SCI (at or above Th 6) [143]. All assisted bladder emptying techniques require low outlet resistance. Even then, high detrusor pressures may still be present. Hence, patients need dedicated education and close urodynamic and urological surveillance [141, 144, 145].

Note: In the literature, including some of the references cited here, the concept "reflex voiding" is sometimes used to cover all three assisted voiding techniques described in this section.

External appliances: Social continence may be achieved by collecting urine during incontinence, for instance using pads. Condom catheters with urine collection devices are a practical method for men [130]. The penile clamp is absolutely contraindicated in case of NDO or low bladder compliance due to the risk of developing high intravesical pressure and pressure sores/necrosis in cases of altered/absent sensations.

3.4.2.2 Neuro-urological rehabilitation

3.4.2.2.1 Bladder rehabilitation including electrical stimulation

The term bladder rehabilitation summarises treatment options that aim to re-establish bladder function in patients with neuro-urological symptoms. Strong contraction of the urethral sphincter and/or pelvic floor, as well as anal dilatation, manipulation of the genital region, and physical activity inhibit micturition in a reflex manner [130, 146]. The first mechanism is affected by activation of efferent nerve fibres, and the latter ones are produced by activation of afferent fibres [105]. Electrical stimulation of the pudendal nerve afferents strongly and inhibits the micturition reflex and detrusor contraction [147]. This stimulation might then support the restoration of the balance between excitatory and inhibitory inputs at the spinal or supraspinal level [130, 148]. Evidence for bladder rehabilitation using electrical stimulation in neurological patients is mainly based on small non-comparative studies with a high risk of bias.

Behavioural therapy and bladder training: In patients with PD, behavioural therapy and bladder training may be considered based on randomised controlled trials (RCTs) with very limited number of patients [149, 150].

Peripheral temporary electrostimulation: Tibial nerve stimulation and transcutaneous electrical nerve stimulation (TENS) might be effective and safe for treating neurogenic LUT dysfunction, but more reliable evidence from well-designed RCTs is required to reach definitive conclusions [148, 151-153]. In post-stroke patients TENS has been shown to effectively improve urodynamic and bladder diary findings as well as QoL [154-156]. In an RCT, transcutaneous tibial nerve home stimulation has proven to significantly reduce bladder diary parameters in women with PD [157]. In acute SCI, TENS is able to achieve bladder neuromodulation via modulation of the autonomous nervous system functions [158]. Greater volumes until full sensation, less detrusor-sphincter dyssynergia and an increased bladder capacity can be found when compared to sham-treated patients [159].

A SR on dorsal genital nerve stimulation showed a higher relative and absolute bladder capacities and inhibition of detrusor hyperactivity in SCI people, although these therapeutic effects may be dependent on the current, amplitude and longer periods of stimulation [160].

Interferential medium frequency current electrical stimulation for SCI patients with American spinal cord injury association impairment scale (AIS) levels B, C and D demonstrated a significant decrease in PVR and volume of urine leakage between catheterisation [161]. Neuromuscular electrical stimulation applied in the sacral area has also improved the performance in symptoms scores in highly selected patients with UI after stroke [155]; however, new RCTs with more patients and longer follow-up are required.

Peripheral temporary electrostimulation combined with pelvic floor muscle training and biofeedback: In MS patients, combining active neuromuscular electrical stimulation with Pelvic Floor Muscle Training (PFMT) and EMG biofeedback can achieve a substantial reduction of neuro-urological symptoms [162, 163]. This treatment combination seems to be more effective than either therapy alone [164, 165]. However, the combination of intravaginal electrostimulation and PFMT was not superior to PFMT alone in reducing UI in women with incomplete SCI [166].

Intravesical electrostimulation: Intravesical electrostimulation can increase bladder capacity and improve bladder filling sensation in patients with incomplete SCI or myelomeningocele (MMC) [167]. In patients with neurogenic detrusor underactivity, intravesical electrostimulation may also improve voiding and reduce residual volume [168, 169].

Repetitive transcranial magnetic stimulation: Although improvement of neuro-urological symptoms has been described in PD, SCI and MS patients, this technique is still under investigation [170]. The role of cortical as well as sacral magnetic stimulation in MS patients with underactive bladder needs to be better defined [171].

Summary: To date, bladder rehabilitation techniques are mainly based on electrical or magnetic stimulation; however, there is a lack of well-designed studies.

3.4.2.3 Drug treatment

A single, optimal, medical therapy for neuro-urological symptoms is not always available. Commonly, a combination of different therapies (e.g. intermittent catheterisation and antimuscarinic drugs) is advised to prevent urinary tract damage and improve long-term outcomes, particularly in patients with a suprasacral SCI or MS [141, 172-174].

3.4.2.3.1 Drugs for storage symptoms

Antimuscarinic drugs: are the first-line choice for treating NDO, increasing bladder capacity and reducing episodes of UI secondary to NDO by the inhibition of parasympathetic pathways [130, 175-181]. Antimuscarinic drugs have been used for many years to treat patients with NDO [179, 180, 182], and the responses of individual patients to antimuscarinic treatment are variable. Despite a meta-analysis confirming the clinical and urodynamic efficacy of antimuscarinic therapy compared to placebo in adult NDO, a more recent integrative review has indicated that the information provided is still too limited for clinicians to be able to match trial data to the needs of individual patients with SCI, mainly due to the lack of use of standardised clinical evaluation tools such as the American Spinal Injury Association bladder diary and validated symptoms score [180, 183].

Higher doses or a combination of antimuscarinic agents may be an option to maximise outcomes in neurological patients [176, 177, 184-187]. However, these drugs have a high incidence of adverse events, which may lead to early discontinuation of therapy. Despite this, NDO patients have generally shown better treatment adherence compared to idiopathic DO patients [188].

Choice of antimuscarinic agent: Oxybutynin [130, 176, 177, 179, 180, 189], trospium [180, 186, 190], tolterodine [191] and propiverine [180, 192] are established, effective and well tolerated treatments even in long-term use [179, 180, 193, 194]. Darifenacin [195, 196] and solifenacin [197] have been evaluated in NDO secondary to SCI and MS [180, 195-197] with results similar to other antimuscarinic drugs. A pilot study using solifenacin in NDO due to PD showed an improvement in UI [198]. Fesoterodine, an active metabolite of tolterodine, has also been introduced; and preliminary results are promising [199, 200]. Favourable results with the new drug imidafenacin have been reported in suprapontine as well as SCI patients [201, 202].

Side effects: Controlled-release antimuscarinics have some minor side effects, e.g. dry mouth [203]. It has been suggested that different ways of administration may help to reduce side effects [204]. Imidafenacine has been safely used in neurological patients with no worsening of cognitive function [201]. Nevertheless, the potential risk of developing dementia should be considered [205].

Beta-3-adrenergic receptor agonists
The role of mirabegron in neuro-urological patients is still unclear [206, 207]. In MS and SCI patients, with very short follow-up, mirabegron has not demonstrated any significant effect on detrusor pressure or cystometric capacity despite the reported improvement in LUT symptoms [208, 209]. A significant subjective improvement in OAB symptoms has also been reported using lower dosages of mirabegron in patients affected by CNS lesions without any negative effects on voiding function [210]. A standard dosage of 50 mg has been found effective with no worsening of cognitive function in patients with PD [211, 212]. Combination therapy with mirabegron and desmopressin in MS patients has shown promising results; however, clinical experience is still very limited in neuro-urological populations [213].

Other drugs
In preliminary studies, improvements in daily incontinence rates, nocturia, daytime and 24-hour voids, as well as the low risk of adverse events, suggest that cannabinoids may be effective and safe in MS patients [214]. A concomitant improvement in OAB symptoms has been reported in male MS patients using daily tadalafil to treat neurogenic erectile dysfunction (ED) [215]. A SR found that desmopressin may be effective for treating nocturia in MS patients; however, adverse events were common, with the included studies being heterogeneous and of low quality [216].

3.4.2.3.2 Drugs for voiding symptoms
Detrusor underactivity: Cholinergic drugs, such as bethanechol and distigmine, have been considered to enhance detrusor contractility and promote bladder emptying, but are not frequently used in clinical practice [217]. Only preclinical studies have documented the potential benefits of cannabinoid agonists for improving detrusor contractility when administered intravesically [218, 219].

Decreasing bladder outlet resistance: α-blockers (e.g. tamsulosin, naftopidil and silodosin) seem to be effective for decreasing bladder outlet resistance, PVR and AD [220-224].

Increasing bladder outlet resistance: Several drugs have shown efficacy in selected cases of mild SUI, but there are no high-level evidence studies in neurological patients [130].

3.4.2.4 Summary of evidence and recommendations for drug treatments

Summary of evidence	**LE**
Long-term efficacy and safety of antimuscarinic therapy for NDO is well documented.	1a
Mirabegron does not improve urodynamic outcomes in NDO patients.	1b
Maximise outcomes for NDO by considering combination therapy.	3

Recommendations	**Strength rating**
Use antimuscarinic therapy as the first-line medical treatment for neurogenic detrusor overactivity.	Strong
Prescribe α-blockers to decrease bladder outlet resistance.	Strong
Do not prescribe parasympathomimetics for underactive detrusor.	Strong

3.4.2.5 Minimally invasive treatment

3.4.2.5.1 Catheterisation

Intermittent self- or third-party catheterisation [225, 226] is the preferred management for neuro-urological patients who cannot effectively empty their bladders [130]. An adequate hand function is an independent risk factor for cessation of intermittent catheterisation (IC) [227].

Sterile IC, as originally proposed by Guttmann and Frankel [225], significantly reduces the risk of UTI and bacteriuria [130, 228, 229], compared with clean IC introduced by Lapides, *et al*., [226]. However, it has not yet been established whether or not the incidence of UTI, other complications and user satisfaction are affected by either sterile or clean IC, coated or uncoated catheters or by any other catheter type [230].

Sterile IC cannot be considered a routine procedure [130, 229] and careful counselling should be employed before commencing IC. In those with MS, commencing IC increases UTI rate over one year by seven fold, without improvement in QoL or symptom score [231]. In addition, in those with SCI, dissatisfaction (and discontinuation) is associated with increased UTI frequency, as well as being of the female sex [232]. It is worth considering patient satisfaction and subsequent compliance when instigating and continuing IC. Shared decision making is imperative, as although IC has better medical outcomes than indwelling catheterisation, in the SCI population it is associated with worse reported QoL compared to indwelling catheters, especially if recurrent (> 4 per year) UTIs complicate management [58, 233]. The use of hydrophilic catheters is associated with a lower rate of UTI [234]. An observational study found that of the 56.9% of patients who used IC 42.1% of patients discontinued IC within 12 months with inconvenience (36%), leakage (20%) and increased infections (19%) listed as the main reasons for the discontinuation [233].

To minimize the risk of UTI in neuro-urological patients, it is important that patient should be adequately taught to self-catheterise [130, 235-239]. The average frequency of catheterisations per day is four to six times [240] and the catheter size most often used is between 12-16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [240]. Ideally, bladder volume at catheterisation should, as a rule, not exceed 400-500 mL.

Indwelling transurethral catheterisation and, to a lesser extent, suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI [130, 241-248]; therefore, both procedures should be avoided, when possible. Silicone catheters are preferred as they are less susceptible to encrustation and because of the high incidence of latex allergy in the neuro-urological patient population [249].

3.4.2.5.2 Summary of evidence and recommendations for catheterisation

Summary of evidence	**LE**
Intermittent catheterisation is the standard treatment for patients who are unable to empty their bladder.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an enhanced risk for UTI.	3

Recommendations	**Strength rating**
Use intermittent catheterisation, whenever possible aseptic technique, as a standard treatment for patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of intermittent catheterisation.	Strong
Avoid indwelling transurethral and suprapubic catheterisation whenever possible.	Strong

3.4.2.5.3 Intravesical drug treatment

To reduce DO, antimuscarinics can also be administered intravesically [204, 250-253]. The efficacy, safety, and tolerability of intravesical administration of 0.1% oxybutynin hydrochloride compared to its oral administration for treatment of NDO has been demonstrated in a recent randomised controlled study [204]. This approach may reduce adverse effects due to the fact that the antimuscarinic drug is metabolised differently [250] and a greater amount is sequestered in the bladder, even more than with electromotive administration [251].

The vanilloids, capsaicin and resiniferatoxin, desensitise the C-fibres for a period of a few months [254, 255]. Clinical studies have shown that resiniferatoxin has limited clinical efficacy compared to botulinum toxin A injections in the detrusor [254].

Although preliminary data suggest that intravesical vanilloids might be effective for treating neurological LUT dysfunction, their safety profile appears to be unfavourable [256]. Currently, there is no indication for the use of these substances, which are not licensed for intravesical treatment.

3.4.2.5.4 Summary of evidence and recommendations for intravesical drug treatment

Summary of evidence	LE
A significant reduction in adverse events was observed for intravesical administration of oxybutynine compared to oral administration.	1a

Recommendation	Strength rating
Offer intravesical oxybutynin to neurogenic detrusor overactivity patients with poor tolerance to the oral route.	Strong

3.4.2.5.5 Botulinum toxin injections in the bladder

Botulinum toxin A causes a long-lasting but reversible chemical denervation that lasts for about nine months [257, 258]. The toxin injections are mapped over the detrusor in a dosage that depends on the preparation used. Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS, SCI and PD in multiple RCTs and meta-analyses [259-262]. Urodynamic studies might be necessary after treatment in patients with maximal filling pressure of > 40 cm H_2O cm in order to monitor the effect of the injections on bladder pressure [263]. Repeated injections seem to be possible without loss of efficacy, even after initial low response rates, based on years of follow-up [257, 264-267]. The clinical efficacy of botulinum toxin A injection in patients with low morbidity after failure of augmentation enterocystoplasty has been demonstrated [268, 269]. A switch between different toxin variations may improve responsiveness [270]. The most frequent side effects are UTIs, urinary retention and haematuria [271]. Intermittent catheterisation may become necessary, this is especially relevant in MS patients as they do not often perform IC prior to intravesical botulinum toxin injections. However, a lower dose of botulinum toxin A (100 U) may reduce the rate of clean IC in MS patients [272]. Rare complications include generalised muscle weakness and AD [271]. Current research focuses on different delivery approaches to injection such as liposome encapsulated botulinum toxin to decrease side effects [273]. Neuro-urological patients with an indwelling catheter and concomitant bladder pain and/or catheter bypass leakage could benefit from intravesical botulinum injections [274].

3.4.2.5.6 Bladder neck and urethral procedures

Reduction of the bladder outlet resistance may be necessary to protect the UUT. This can be achieved by chemical denervation of the sphincter or by surgical interventions (bladder neck or sphincter incision or urethral stent – Section 3.4.3.1). Incontinence may result and can be managed by external devices (Section 3.4.2.1).

Botulinum toxin A: This can be used to treat DSD effectively by injecting the sphincter at a dose that depends on the preparation used. The dyssynergia is abolished only for a few months, necessitating repeat injections. The efficacy of this treatment has been reported to be high with few adverse effects [275-277]. However, a recent SR concluded that, because of limited evidence, future RCTs assessing the effectiveness of botulinum toxin A injections also need to address the uncertainty about the optimal dose and mode of injection [278]. In addition, this therapy is not licensed.

Balloon dilatation: Favourable immediate results were reported [279], but there have been no further reports since 1994; therefore, this method is no longer recommended.

Increasing bladder outlet resistance: This can improve the continence condition. However, despite early positive results with urethral bulking agents, a relative early loss of continence is reported in patients with neuro-urological disorders [130, 280, 281].

Urethral inserts: Urethral plugs or valves for the management of (female) stress incontinence have not been applied in neuro-urological patients. The experience with active pumping urethral prosthesis for treatment of the underactive or acontractile detrusor were disappointing [282].

3.4.2.5.7 Summary of evidence and recommendations for botulinum toxin A injections and bladder neck procedures

Summary of evidence	LE
Botulinum toxin A has been proven effective in patients with neuro-urological disorders due to MS or SCI in multiple RCTs and meta-analyses.	1a
Bladder neck incision is indicated only for secondary changes (fibrosis) at the bladder neck.	4

Recommendations	Strength rating
Use botulinum toxin injection in the detrusor to reduce neurogenic detrusor overactivity in multiple sclerosis or spinal cord injury patients if antimuscarinic therapy is ineffective.	Strong
Use bladder neck incision as it is effective in a fibrotic bladder neck.	Strong

*3.4.3 **Surgical treatment***

There is considerable heterogeneity in outcome parameters and definitions of cure used to report on outcomes of surgical interventions for SUI in neuro-urological patients [283]. The heterogeneity of outcome reporting makes it difficult to interpret and compare different studies and therapies. A consistent comparison of the outcomes of therapy can only be made after standardisation of outcome parameters and definitions of cure or success; therefore, it would seem prudent to develop a core outcome set (COS) for use in UI research in neuro-urological patients [283]. Until such a COS is developed it would seem feasible to use both a subjective and objective outcome parameter and the combination of both to define cure [283]. Due to the importance of QoL for neuro-urological patients a disease-specific QoL questionnaire or a bother questionnaire validated for neuro-urological patients should be used as the subjective outcome parameter [283].

3.4.3.1 Bladder neck and urethral procedures

Increasing the bladder outlet resistance has the inherent risk of causing high intravesical pressure. Procedures to treat sphincteric incontinence are therefore suitable only when the detrusor activity can be controlled and when no significant reflux is present. A simultaneous bladder augmentation and IC may be necessary [130].

Urethral sling: Various materials have been used for this procedure with enduring positive results. The procedure is established in women with the ability to self-catheterise [130, 284-287]. There is growing evidence that synthetic slings can be used effectively with acceptable medium to long-term results and minimal morbidity in neurological patients [288, 289]. Besides the pubovaginal sling, which has been considered the procedure of choice in this subgroup of patients, recent reports suggest that both the transobturator and the retropubic approaches may also be considered, with similar failure rates and a reduction in the need for IC. However, for both approaches a higher incidence of *de novo* urgency was reported [289, 290]. A SR reporting on 100 women treated with an autologous fascial sling (in five studies), with a follow-up of 24 to 52 months, had a success rate ranging from 75% to 100%. In the same review, 80 women in four studies received a synthetic sling (TVT, TOT or mini-sling), with a follow-up ranged from 46 to 119 months and reported a success rate ranging from 75% to 85%. Complications were the need to perform IC, mesh erosion or extrusion requiring partial or total removal and retropubic haematoma [291].

In men, both autologous and synthetic slings may also be an alternative [292-296]. A SR reported 84 men treated with autologous puboprostatic slings or various types of synthetic tapes [291]. The cure rate ranged from 29% to 71% at a follow-up of 12 to 36 months. Complications included haematoma, tape infection or erosion into urethra and difficulty to perform IC [291].

Artificial urinary sphincter (AUS): This device was introduced by Light and Scott for patients with neuro-urological disorders [297]. It has stood the test of time and acceptable long-term outcomes can be obtained [298]. Implantation of AUS is the most often performed procedure for neurogenic SUI in both men and women and accounts for 49% of all the reported neurogenic SUI procedures (67 % in men and 33% in women) with a high success/improvement rate [291]. However, the complication rates and re-operation rates are higher than in non-neurogenic patient groups (up to 60%), so it is advisable that patients are conscientiously informed about the success rates as well as the possible need for re-intervention [299, 300]. In a case series with 25 years follow-up only 7.1% of patients were revision free at twenty years [301]. Re-interventions are commonly due to mechanical failure, urethral atrophy or erosion and infection.

There is growing interest in the use of this device in women with development of laparoscopic and robot-assisted approaches via an anterior or a posterior access to the bladder neck [302-305], which may reduce the infection and erosion rate. Although from a single institution series, long-term surgical results are now available and support the potentially prominent role of AUS placement in female patients with neurogenic SUI [291, 306-308].

Long-term surgical and patient-reported outcomes are needed to determine the role of AUS placement in female patients with neurogenic SUI [306].

Adjustable continence device - ProACT/ACT®: The efficacy of this device has been reported mainly in post-prostatectomy incontinence. A marginally lower cure rate has been reported in neurological patients when compared to non-neurological patients [309]. A retrospective study in neuro-urological patients reported a low rate of efficacy and high complication rate for this device [310].

Functional sphincter augmentation: Transposing the gracilis muscle to the bladder neck [311] or proximal urethra [312], can enable the possible creation of a functional autologous sphincter by electrical stimulation [311-313]; therefore, raising the prospect of restoring control over the urethral closure.

Bladder neck and urethra reconstruction: The classical Young-Dees-Leadbetter procedure [314] for bladder neck reconstruction in children with bladder exstrophy, and Kropp urethra lengthening [315] improved by Salle [316], are established methods to restore continence provided that IC is practiced and/or bladder augmentation is performed [130, 317].

Endoscopic techniques for treating anatomic bladder outlet obstruction [318]:

- *Transurethral resection of the prostate* is indicated in male patients with refractory LUT symptoms due to benign prostatic obstruction. Special consideration should be given to pre-operative abnormal sphincter function which can lead to *de novo* or persistent UI [319, 320].
- *Bladder neck resection* is indicated in patients with high PVR and when a prominent obstruction of the sclerotic ring in the bladder neck is identified during cystoscopy. The resection can be performed between the three or nine o'clock position or full circle [321].
- *Urethrotomy* is indicated in patients with urethral strictures. Cold knife or neodymium:YAG contact laser urethrotomy at the twelve o'clock position can be performed [322, 323]. In recurrent strictures, open surgery should be considered.
- *Sphincterotomy* has been shown to be an efficient technique for the resolution of AD, hydronephrosis and recurrent UTI, and for decreasing detrusor pressure, PVR and vesicoureteral reflux. It is irreversible and should be limited to men who are able to wear a condom catheter. By staged incision, bladder outlet resistance can be reduced without completely losing the closure function of the urethra [129, 130, 324]. The incision with less complications, is the twelve o'clock sphincterotomy with cold knife [325] or neodymium:YAG laser [326]. Sphincterotomy needs to be repeated at regular intervals in many patients [327], but it is efficient and does not cause severe adverse effects [129, 279]. Secondary narrowing of the bladder neck may occur, for which combined bladder neck incision might be considered [328].

Bladder neck incision: This is indicated only for secondary changes at the bladder neck (fibrosis) [129, 329]. This procedure is not recommended in patients with detrusor hypertrophy, which causes thickening of the bladder neck [129].

Stents: Implantation of urethral stents results in continence being dependent on adequate closure of the bladder neck [130]. The results are comparable with sphincterotomy and the stenting procedure has a shorter duration of surgery and hospital stay [330, 331]. However, the costs [129], possible complications and re-interventions [332, 333] are limiting factors in their use [334-337].

3.4.3.2 Denervation, deafferentation, sacral neuromodulation

Sacral anterior root stimulation (SARS) is aimed at producing detrusor contraction. The technique was developed by Brindley [338] and is only applicable to complete lesions above the implant location, as its stimulation amplitude is over the pain threshold. The urethral sphincter efferents are also stimulated, but because the striated muscle relaxes faster than the smooth muscle of the detrusor, so-called "post-stimulus voiding" occurs. This approach has been successful in highly selected patients [339-341]. Although it has been shown that detrusor pressure during SARS decreases over time, the changes do not seem to be clinically relevant during the first decade after surgery [342]. By changing the stimulation parameters, this method can also induce defecation or erection. A recent study reported that Charcot spinal arthropathy should be considered as a potential long-term complication of SARS, leading to spinal instability and to SARS dysfunction [343].

Sacral rhizotomy, also known as sacral deafferentation, has achieved some success in reducing DO [344-346], but nowadays, it is used mostly as an adjuvant to SARS [339, 347-350]. Alternatives to rhizotomy are sought in this treatment combination [351-353].

There is growing evidence, based mostly on case series, on the use of sacral neuromodulation for treating neuro-urological symptoms, but due to the lack of RCTs it remains unclear which neurological patients are most suitable [354-356]. With the development of MRI-compatible pulse generators and leads, the avoidance of this procedure in patients needing this imaging technique for their follow-up is no longer required.

Other neuromodulation techniques like deep brain stimulation in PD patients may have beneficial effects in the LUT but these depend on the site of stimulation and although prospective, specifically designed studies are needed in neuro-urological patients [357].

3.4.3.3 Bladder covering by striated muscle

When the bladder is covered by striated muscle, that can be stimulated electrically, or ideally that can be contracted voluntarily, voiding function can be restored to an acontractile bladder. The rectus abdominis [358] and latissimus dorsi [359] have been used successfully in patients with neuro-urological symptoms [360, 361].

3.4.3.4 Bladder augmentation

The aim of auto-augmentation (detrusor myectomy) is to reduce DO or improve low bladder compliance. The advantages are low surgical burden, low rate of long-term adverse effects, positive effect on patient QoL, and it does not preclude further interventions [129, 130, 362-365].

Replacing or expanding the bladder by intestine will improve bladder compliance and at least reduce the pressure effect of DO [366, 367]. Improved QoL and stable renal function has been reported during long-term follow-up [368]. Patients performing IC with augmentation cystoplasty had better urinary function and satisfaction with their urinary symptoms compared to patients performing IC with or without botulinum toxin treatment [369]. Long-term complications included bladder perforation (1.9%), mucus production (12.5%), metabolic abnormalities (3.35%), bowel dysfunction (15%), and stone formation (10%) [368].

The procedure should be used with caution in patients with neuro-urological symptoms, but may become necessary if all less-invasive treatment methods have failed. Special attention should be paid to patients with pre-operative renal scars since metabolic acidosis can develop [370]. Bladder substitution with bowel after performing a supratrigonal cystectomy [367], to create a low-pressure reservoir, is indicated in patients with a severely thick and fibrotic bladder wall [130]. Intermittent catheterisation may become necessary after this procedure. The long-term scientific evidence shows that bladder augmentation is a highly successful procedure that stabilises renal function and prevents anatomical deterioration; however, lifelong follow-up is essential in this patient group given the significant morbidity associated with this procedure [368, 371, 372].

3.4.3.5 Urinary diversion

When no other therapy is successful, urinary diversion must be considered for the protection of the UUT and for the patient's QoL [130].

Continent diversion: This should be the first choice for urinary diversion. Patients with limited dexterity may prefer a stoma instead of using the urethra for catheterisation. For cosmetic reasons, the umbilicus is often used for the stoma site [373-379]. A SR of the literature concluded that continent catheterisable tubes/stomas are an effective treatment option in neuro-urological patients unable to perform intermittent self-catheterisation through the urethra [380]. However, the complication rates were significant with 85/213 post-operative events requiring re-operation [380]. Tube stenosis occurred in 4-32% of the cases. Complications related to concomitant procedures (augmentation cystoplasty, pouch) included neovesicocutaneous fistulae (3.4%), bladder stones (20-25%), and bladder perforations (up to 40% in one case series). In addition, data comparing HRQoL before and after surgery were not reported [380].

Incontinent diversion: If catheterisation is impossible, incontinent diversion with a urine-collecting device is indicated. Ultimately, it could be considered in patients who are wheelchair bound or bed-ridden with intractable and untreatable incontinence, in patients with LUT destruction, when the UUT is severely compromised, and in patients who refuse other therapy [130]. An ileal segment is used for the deviation in most cases [130, 381-384]. Patients gain better functional status and QoL after surgery [385]. Concomitant cystectomy to avoid pyocystitis may be advisable [386]. All procedures can be done robotically [387].

Undiversion: Long-standing diversions may be successfully undiverted or an incontinent diversion changed to a continent one with the emergence of new and better techniques for control of detrusor pressure and incontinence [130]. The patient must be carefully counselled and must comply meticulously with the instructions [130]. Successful undiversion can then be performed [388].

In a prospective observational study (n=1,479), QoL was investigated in neuro-urological patients using four different bladder management options. It is the first study to focus on PROMS and noted that surgery was associated with fewer bladder management difficulties and a better QoL [58].

3.4.3.6 Summary of evidence and recommendations for surgical treatment

Summary of evidence	LE
Bladder augmentation is an effective option to decrease detrusor pressure and increase bladder capacity, when all less-invasive treatment methods have failed.	3
Urethral sling placement is an established procedure, with acceptable mid- to long-term results, in women with the ability to self-catheterise.	3
Artificial urinary sphincter insertion is the most frequently offered option to treat neurogenic SUI with acceptable long-term outcomes, in males. The complication and re-operation rates are higher in neuro-urological patients; therefore, patients must be adequately informed regarding the success rates as well as the complications that may occur following the procedure.	3

Recommendations	Strength rating
Perform bladder augmentation in order to treat refractory neurogenic detrusor overactivity.	Strong
Place an autologous urethral sling as first-line treatment in female patients with neurogenic stress urinary incontinence (SUI) who are able to self-catheterise.	Strong
Place a synthetic urethral sling, as an alternative to autologous urethral slings, in selected female patients with neurogenic SUI who are able to self-catheterise.	Weak
Insert an artificial urinary sphincter in selected female patients with neurogenic SUI; however, patients should be referred to experienced centres for the procedure.	Weak
Insert an artificial urinary sphincter in male patients with neurogenic SUI.	Strong

3.5 Urinary tract infection in neuro-urological patients

3.5.1 Epidemiology, aetiology and pathophysiology

Urinary tract infection is the onset of signs and/or symptoms accompanied by laboratory findings of a UTI (bacteriuria, leukocyturia and positive urine culture) [374]. There are no evidence-based cut-off values for the quantification of these findings. The published consensus is that a significant bacteriuria in persons performing IC is present with > 10^2 cfu/mL, > 10^4 cfu/mL in clean-void specimens and any detectable concentration in suprapubic aspirates. Regarding leukocyturia, ten or more leukocytes in centrifuged urine samples per microscopic field (400x) are regarded as significant [374].

The pathogenesis of UTI in neuro-urological patients is multifactorial. Male gender seems to be a risk factor for febrile UTI [389]. Several etiological factors have been described: altered intrinsic defence mechanisms, impaired washout and catheterisation [390]. Poor glycemic control has also been established as a risk factor for UTI in women with type 1 diabetes [391]. However, the exact working mechanisms remain unknown. The presence of asymptomatic bacteriuria in SCI patients is higher than in the general population and varies depending on bladder management. Prevalence of bacteriuria in those performing clean IC varies from 23%-89% [392]. Sphincterotomy and condom catheter drainage has a 57% prevalence [393]. Asymptomatic bacteria should not be routinely screened for in this population [394] but a nomogram can be a helpful tool for early prediction of UTIs [395] .

Individuals with neuro-urological symptoms, especially those with SCI, may have other signs and symptoms in addition to or instead of traditional signs and symptoms of a UTI in able-bodied individuals. Other problems, such as AD, may develop or worsen due to a UTI [234]. The most common signs and symptoms suspicious of a UTI in those with neuro-urological disorders are fever, new onset or increase in incontinence, including leaking around an indwelling catheter, increased spasticity, malaise, lethargy or sense of unease, cloudy urine with increased urine odour, discomfort or pain over the kidney or bladder, dysuria, or AD [234, 396]. New incontinence is the most specific symptom, whereas cloudy and foul-smelling urine has the highest positive predictive value for UTI diagnosis [397].

3.5.2 Diagnostic evaluation

Urine culture and urinalysis are the optimum tests for the diagnosis of UTI in neuro-urological patients. A dipstick test may be more useful to exclude rather than to prove UTI [398, 399]. As bacterial strains and resistance patterns in persons with neuro-urological disorders may differ from those of able-bodied patients, microbiologic testing is mandatory [400].

3.5.3 ***Disease management***

Bacteriuria in patients with neuro-urological disorders should not be treated. Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving the outcome [401]. Urinary tract infections in persons with neuro-urological disorders are by definition a complicated UTI; therefore, single-dose treatment is not advised. There is no consensus in the literature about the duration of treatment as it depends on the severity of the UTI and the involvement of the kidneys and the prostate. Generally, a five to seven day course of antibiotic treatment is advised, which can be extended up to fourteen days according to the extent of the infection [401]. The choice of antibiotic therapy should be based on the results of the microbiologic testing. If immediate treatment is mandatory (e.g., fever, septicaemia, intolerable clinical symptoms, extensive AD), the choice of treatment should be based on local and individual resistance profiles [402]. In patients with afebrile UTI, an initial non-antibiotic treatment may be justified [403, 404].

3.5.3.1 *Recurrent UTI*

Recurrent UTI in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem, e.g., high bladder pressure during storage and voiding, incomplete voiding or bladder stones. The improvement of bladder function, by treating DO by botulinum toxin A injection in the detrusor [405], and the removal of bladder stones or other direct supporting factors, especially indwelling catheters, as early as possible, are mandatory [400].

3.5.3.2 *Prevention*

If the improvement of bladder function and removal of foreign bodies/stones is not successful, additional UTI prevention strategies should be utilised. In a meta-analysis the use of hydrophilic catheters was associated with a lower rate of UTI [234]. Bladder irrigation has not been proven effective [406].

Various medical approaches have been tested for UTI prophylaxis in patients with neuro-urological disorders. The benefit of cranberry juice or probiotics for the prevention of UTI could not be demonstrated in RCTs [407, 408]. Methenamine hippurate is not effective in individuals with neuro-urological symptoms [409]. There is no sufficient evidence to support the use of L-methionine for urine acidification to prevent recurrent UTIs [410]. There is only weak evidence that oral immunotherapy reduces bacteriuria in patients with SCI [411] and that recurrent UTIs are reduced [412]. Low-dose, long-term, antibiotic prophylaxis can reduce UTI frequency, but increases bacterial resistance and is therefore not recommended [401].

Weekly cycling of antibiotic prophylaxis provided long-term positive results, but the results of this trial need to be confirmed in further studies [413]. Another possible future option, the inoculation of apathogenic *Escherichia coli* strains into the bladder, has provided positive results in initial studies, but because of the paucity of data [414], cannot be recommended as a treatment option. There is initial evidence that homeopathic treatment can decrease UTI frequency [415]. In addition, intravesical gentamycin instillations can reduce UTI frequency without increasing the number of multi-resistant bacteria [416].

In summary, based on the criteria of evidence-based medicine, there is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations. Therefore, individualised concepts should be taken into consideration, including immunostimulation, phytotherapy and complementary medicine [417]. Prophylaxis in patients with neuro-urological disorders is important to pursue, but since there are no data favouring one approach over another, prophylaxis is essentially a trial-and-error approach.

3.5.4 ***Summary of evidence and recommendations for the treatment of UTI***

Summary of evidence	**LE**
Treatment of asymptomatic bacteriuria results in significantly more resistant bacterial strains without improving patient outcome.	1a
Low-dose, long-term, antibiotic prophylaxis does not reduce UTI frequency, but increases bacterial resistance.	2a
Recurrent UTIs in patients with neuro-urological disorders may indicate suboptimal management of the underlying functional problem. Improvement of bladder function as early as possible is mandatory.	3
There is currently no preventive measure for recurrent UTI in patients with neuro-urological disorders that can be recommended without limitations.	3

Recommendations	Strength rating
Do not screen for or treat asymptomatic bacteriuria in patients with neuro-urological disorders.	Strong
Avoid the use of long-term antibiotics for recurrent urinary tract infections (UTIs).	Strong
In patients with recurrent UTIs, optimise treatment of neuro-urological symptoms and remove foreign bodies (e.g., stones, indwelling catheters) from the urinary tract.	Strong
Individualise UTI prophylaxis in patients with neuro-urological disorders as there is no optimal prophylactic measure available.	Strong

3.6 Sexual function and fertility

These Guidelines specifically focus on sexual dysfunction and infertility in patients with a neurological disease [418, 419]. Non-neurogenic, male sexual dysfunction and infertility are covered in separate EAU Guidelines [420, 421]. In neuro-urological patients sexual problems can be identified at three levels: primary (direct neurological damage), secondary (general physical disabilities) and tertiary (psychosocial and emotional issues) sexual dysfunction [422]. Adopting a systematic approach, such as the PLISSIT model (Permission, Limited Information, Specific Suggestions and Intensive Therapy) [423], provides a framework for counselling and treatment involving a stepwise approach to the management of neurogenic sexual dysfunction. Sexual dysfunction is associated with neurogenic LUT dysfunction in patients with MS [424] and SB [425]. Although various PROMs are available to evaluate sexual function, the evidence for good PROMs is limited and studies with high methodological quality are needed [75].

*3.6.1 **Erectile dysfunction***

3.6.1.1 Phosphodiesterase type 5 inhibitors (PDE5Is)

Phosphodiesterase type 5 inhibitors (PDE5Is) are recommended as first-line treatment in neurogenic ED [418, 419]. In SCI patients, tadalafil, vardenafil and sildenafil have all improved retrograde ejaculation and improved erectile function and satisfaction on IIEF-15. Tadalafil 10 mg was shown to be more effective than sildenafil 50 mg. All currently available PDE5Is appear to be effective and safe, although there are no high-level evidence studies in neuro-urological patients investigating the efficacy and side effects across different PDE5Is, dosages and formulations [426].

For MS patients two studies reported significant improvement in ED when using sildenafil and tadalafil [427, 428] however, another study showed no improvement in ED with sildenafil [429]. One study found a significant improvement in ED in SB patients when using sildenafil [430].

In PD normal erectile function was described in over half of the patients using sildenafil 100 mg and a significant improvement in IIEF-15 score was found compared to placebo. While most neuro-urological patients require long-term therapy for ED some have a low compliance rate or stop therapy because of side effects [431, 432], most commonly headache and flushing [419]. In addition, PDE5Is may induce relevant hypotension in patients with tetraplegia/high-level paraplegia and multiple system atrophy [431, 432]. As a prerequisite for successful PDE5I-therapy, some residual nerve function is required to induce erection. Since many patients with SCI use on-demand nitrates for the treatment of AD, they must be counselled that PDE5Is are contraindicated when using nitrate medication.

3.6.1.2 Drug therapy other than PDE5Is

Fampridine to treat neurogenic spasticity has been shown to be beneficial in improving ED in two domains of the IIEF-15 in SCI and MS patients, however, with a significant discontinuation rate due to severe adverse events [433]. Sublingual apomorfine was shown to have poor results on ED in SCI patients and side-effects in half of the patients [434]. In PD, pergolide mesylate showed a significant improvement in IIEF-15 scores up to twelve months follow-up [435].

3.6.1.3 Mechanical devices

Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular [436-440].

3.6.1.4 Intracavernous injections and intraurethral application

Patients not responding to oral drugs may be offered intracavernous injections (alprostadil, papaverine and phentolamine) that have been shown to be effective in a number of neurological conditions, including SCI, MS, and diabetes mellitus [441-447], but their use requires careful dose titration and some precautions. Complications of intracavernous drugs include pain, priapism and corpora cavernosa fibrosis.

Intracavernous vasoactive drug injection is the first-line therapeutic option in patients taking nitrate medications, as well as those with concerns about drug interactions with PDE5Is, or in whom PDE5Is are ineffective. The impact of intracavernous injections on ejaculation and orgasmic function, their early

use for increasing the recovery rate of a spontaneous erection, and their effectiveness and tolerability in the long-term are unclear [431]. Intra-urethral alprostadil application is an alternative, but less effective, route of administration [443, 448].

3.6.1.5 Sacral neuromodulation

Sacral neuromodulation for LUT dysfunction may improve sexual function; however, high level evidence studies are lacking.

3.6.1.6 Penile prostheses

Penile prostheses may be considered for treatment of neurogenic ED when all conservative treatments have failed. At a mean follow-up of seven years, 83.7% of patients with SCI were able to have sexual intercourse [419]. Serious complications, including infection and prosthesis perforation, may occur in about 10% of patients, depending on implant type [449-451].

3.6.1.7 Summary of evidence and recommendations for erectile dysfunction

Summary of evidence	**LE**
The long-term efficacy and safety of oral PDE5Is for the treatment of ED is well documented.	1b
Intracavernous vasoactive drug injections have been shown to be effective in a number of neurological conditions, including SCI and MS; however, their use requires careful dose titration and precautions.	3
Mechanical devices (vacuum tumescence devices and penile rings) may be effective but are less popular.	3
Reserve penile prostheses for selected patients, those in which all conservative treatments have failed, with neurogenic ED.	4

Recommendations	**Strength rating**
Prescribe oral phosphodiesterase type 5 inhibitors as first-line medical treatment in neurogenic erectile dysfunction (ED).	Strong
Give intracavernous injections of vasoactive drugs (alone or in combination) as second-line medical treatment in neurogenic ED.	Strong
Offer mechanical devices such as vacuum devices and rings to patients with neurogenic ED.	Strong

*3.6.2 **Male fertility***

Male fertility can be compromised in the neurological patient by ED, ejaculation disorder, impaired sperm quality or various combinations of these three disorders. Among the major conditions contributing to neurogenic infertility are pelvic and retroperitoneal surgery, diabetes mellitus, SB, MS and SCI [452]. Erectile dysfunction is managed as described previously. Retrograde ejaculation may be reversed by sympathomimetic agents contracting the bladder neck, including imipramine, ephedrine, pseudoephedrine, and phenylpropanolamine [452]. The use of a balloon catheter to obstruct the bladder neck may be effective in obtaining antegrade ejaculation [453]. If antegrade ejaculation is not achieved, the harvest of semen from the urine may be considered [454].

Prostatic massage is safe and easy to use for obtaining semen in men with lesions above Th 10 [455]. In several patients, vibrostimulation or transrectal electroejaculation are needed for sperm retrieval [452, 456, 457]. Semen retrieval is more likely with vibrostimulation in men with lesions above Th 10 [458-460]. In men with SCI, especially at or above Th 6, AD might occur during sexual activity and ejaculation [461, 462]; patients at risk and fertility clinics must be informed and aware of this potentially life-threatening condition. In SCI patients the use of oral midodrine can improve sperm retrieval at vibrostimulation [463].

In men with MS, use of disease modifying drugs during the conception phase, has not been associated with altered pregnancy outcomes [464]. Surgical procedures, such as, microsurgical epididymal sperm aspiration or testicular sperm extraction, may be used if vibrostimulation and electroejaculation are not successful [465, 466]. Pregnancy rates in patients with SCI are lower than in the general population, but since the introduction of intracytoplasmic sperm injection, men with SCI now have a good chance of becoming biological fathers [467-469].

3.6.2.1 Sperm quality and motility

The following has been reported on sperm quality and motility:

- bladder management with clean IC may improve semen quality compared to indwelling catheterisation, reflex voiding or bladder expression [470];
- in SCI patients sperm quality decreases at the early post traumatic phase demonstrating lower spermatozoid vitality (necrospermia), reduced motility (asthenospermia) and leucospermia [465];
- long-term valproate treatment for epilepsy negatively influences sperm count and motility [471];
- vibrostimulation produces samples with better sperm motility than electrostimulation [472, 473];
- electroejaculation with interrupted current produces better sperm motility than continuous current [474];
- freezing of sperm is unlikely to improve fertility rates in men with SCI [475].

3.6.2.2 Summary of evidence and recommendations for male fertility

Summary of evidence	**LE**
Vibrostimulation and transrectal electroejaculation have been shown to be effective for sperm retrieval in neuro-urological patients.	1b
Surgical procedures, such as, microsurgical epididymal sperm aspiration or testicular sperm extraction, may be used if vibrostimulation and electroejaculation are not successful.	3
In men with SCI at or above Th 6, AD might occur during sexual activity and ejaculation.	3

Recommendations	**Strength rating**
Perform vibrostimulation and transrectal electroejaculation for sperm retrieval in men with spinal cord injury.	Strong
Perform microsurgical epididymal sperm aspiration, testicular sperm extraction and intracytoplasmic sperm injection after failed vibrostimulation and/or transrectal electroejaculation in men with spinal cord injury.	Strong
Counsel men with spinal cord injury at or above Th 6 and fertility clinics about the potentially life-threatening condition of autonomic dysreflexia.	Strong

3.6.3 ***Female sexuality***

The most relevant publications on neurogenic female sexual dysfunction are in women with SCI and MS. After SCI, about 65-80% of women continue to be sexually active, but to a much lesser extent than before the injury, and about 25% report a decreased satisfaction with their sexual life [476-478]. Although sexual dysfunction is very common in women with MS, it is still often overlooked by medical professionals [479, 480]. A vast majority of female SB patients considered information about sexuality from their physicians insufficient [481]. Women with SCI reported dissatisfaction with the quality and quantity of sexuality-related rehabilitation services and were less likely to receive sexual information than men [482-484].

The greatest physical barrier to sexual activity is UI. A correlation has been found between the urodynamic outcomes of low bladder capacity, compliance and high maximum detrusor pressure and sexual dysfunction in MS patients. Problems with positioning and spasticity affect mainly tetraplegic patients. Peer support may help to optimise the sexual adjustment of women with SCI in achieving a more positive self-image, self-esteem and feelings of being attractive to themselves and others [476, 485-487].

The use of specific drugs for sexual dysfunction is indicated to treat inadequate lubrication. Data on sildenafil for treating female sexual dysfunction are poor and controversial [419]. Although good evidence exists that psychological interventions are effective in the treatment of female hypoactive sexual desire disorder and female orgasmic disorder [488], there is a lack of high-level evidence studies in the neurological population.

Neurophysiological studies have shown that women with the ability to perceive Th 11-L2 pin-prick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm are more prevalent in women with SCI who have preserved the sacral reflex arc (S2-S5), even when it has not been shown in an individual woman that a specific level and degree of lesion is the cause of a particular sexual dysfunction. In SCI women with a complete lesion of the sacral reflex, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions [482, 489, 490].

Sacral neuromodulation for LUT dysfunction may improve sexual function but high-evidence studies are lacking [419].

3.6.4 *Female fertility*

There are few studies on female fertility in neurological patients. More than a third (38%) of women with epilepsy had infertility and the relevant predictors were exposure to multiple (three or more) antiepileptic drugs, older age and lower education [491].

Although it seems that the reproductive capacity of women with SCI is only temporarily affected by SCI with cessation of menstruation for approximately six months after SCI [492], there are no high-level evidence studies. About 70% of sexually active women use some form of contraception after injury, but fewer women use the birth control pill compared to before their injury [493].

Women with SCI are more likely to suffer complications during pregnancy, labour and delivery compared to able-bodied women. Complications of labour and delivery include bladder problems, spasticity, pressure sores, anaemia, and AD [494-498]. Obstetric outcomes include higher rates of Caesarean sections and an increased incidence of low birth-weight babies [493, 496-498].

Epidural anaesthesia is chosen and effective for most patients with AD during labour and delivery [499, 500].

There is very little published data on women's experience of the menopause following SCI [501]. Women with MS who plan a pregnancy should evaluate their current drug treatment with their treating physician [502-504]. Clinical management should be individualised to optimise both the mother's reproductive outcomes and MS course [502, 503, 505].

3.6.4.1 *Summary of evidence and recommendation for female sexuality and fertility*

Summary of evidence	**LE**
Data on specific drugs for treating female sexual dysfunction are poor and controversial.	4
There are limited numbers of studies on female fertility in neurological patients, clinical management should be individualised to optimise both the mother's reproductive outcomes and medical condition.	4

Recommendations	**Strength rating**
Do not offer medical therapy for the treatment of neurogenic sexual dysfunction in women.	Strong
Take a multidisciplinary approach, tailored to individual patient's needs and preferences, in the management of fertility, pregnancy and delivery in women with neurological diseases.	Strong

3.7 Follow-up

3.7.1 *Introduction*

Neuro-urological disorders are often unstable, and the symptoms may vary considerably, even within a relatively short period. Regular follow-up is therefore necessary to assess the UUT [128].

Depending on the type of the underlying neurological pathology and the current stability of the neuro-urological symptoms, the interval between initial investigations and control diagnostics may vary and, in many cases, should not exceed one to two years. In high-risk neuro-urological patients this interval should be much shorter. Urinalysis should be performed only when patients present with symptoms [506]. The UUT should be checked by ultrasonography at regular intervals in high-risk patients; about once every six months [6, 507]. In these patients, physical examination and urine laboratory should take place every year [6, 507]. In MS patients higher scores on the Expanded Disability Status Scale (EDSS) are associated with risk factors for UUT deterioration [508]. A urodynamic investigation should be performed as a diagnostic baseline, and repeated during follow-up, more frequently in high-risk patients [6, 507]. In addition, bladder wall thickness can be measured on ultrasonography as an additional risk assessment for upper tract damage [509], although a 'safe' cut-off threshold for this has not been agreed [510]. The utility of DMSA (dimercaptosuccinic acid) for follow-up of neuro-urological patients has not been fully evaluated [511]. Any significant clinical change warrants further, specialised, investigation [6, 507]. However, there is a lack of high level evidence studies on this topic and every recommendation must be viewed critically in each individual neuro-urological patient [128].

The increased prevalence of muscle invasive bladder cancer in neuro-urological patients also warrants long-term follow-up [512]. The exact frequency of cystoscopy with or without cytology remains unknown, but presence of risk factors similar to the general population should trigger further investigation [506].

Adolescent patients with neurological pathology are at risk of being lost to follow-up during the transition to

adulthood. It is important that a standardised approach during this transition is adopted to improve follow-up and specific treatment during adult life [513].

*3.7.2 **Summary of evidence and recommendations for follow-up***

Summary of evidence	LE
Neuro-urological disorders are often unstable, and the symptoms may vary considerably; therefore, regular follow-up is necessary.	4

Recommendations	Strength rating
Assess the upper urinary tract at regular intervals in high-risk patients.	Strong
Perform a physical examination and urine laboratory every year in high-risk patients.	Strong
Any significant clinical changes should instigate further, specialised, investigation.	Strong
Perform urodynamic investigation as a mandatory baseline diagnostic intervention in high-risk patients at regular intervals.	Strong

3.8 Conclusions

Neuro-urological disorders have a multi-faceted pathology. They require an extensive and specific diagnosis before one can embark on an individualised therapy, which takes into account the medical and physical condition of the patient and the patient's expectations about their future. The urologist can select from a wealth of therapeutic options, each with its own pros and cons. Notwithstanding the success of any therapy embarked upon, close surveillance is necessary for the patient's entire life.

These Guidelines offer you expert advice on how to define the patient's neuro-urological symptoms as precisely as possible and how to select, together with the patient, the appropriate therapy. This last choice, as always, is governed by the golden rule: as effective as needed, as non-invasive as possible.

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5. CONFLICT OF INTEREST

All members of the Neuro-urology working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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1. INTRODUCTION

1.1 Aim and scope

This overview represents the updated European Association of Urology (EAU) Guidelines for Non-muscle-invasive Bladder Cancer (NMIBC), TaT1 and carcinoma *in situ* (CIS). The information presented is limited to urothelial carcinoma, unless specified otherwise. The aim is to provide practical recommendations on the clinical management of NMIBC with a focus on clinical presentation and recommendations.

Separate EAU Guidelines documents are available addressing upper tract urothelial carcinoma (UTUC) [1], muscle-invasive and metastatic bladder cancer (MIBC) [2] and primary urethral carcinoma [3]. It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a pathologist, and a statistician. Members of this Panel have been selected based on their expertise and to represent the professionals treating patients suspected of suffering from bladder cancer. In the course of 2021 two patient representatives have formally joined the NMIBC Panel. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the latest publication dating to 2022 [4], as are a number of translations of all versions of the EAU NMIBC Guidelines. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU Guidelines on Bladder Cancer were first published in 2000. This 2022 NMIBC Guidelines document presents a limited update of the 2021 publication.

1.4.2 Summary of changes

Additional data has been included throughout this document text. In particular in Chapters/Sections:

- 5.4 Imaging – with the introduction of Vesical Imaging-Reporting and Data System [VI-RADS]).
- 5.7.3 Surveillance of non-muscle-invasive bladder cancer – inclusion of urine biomarkers in a surveillance strategy of an individual patient.
- 5.8 Cystoscopy – inclusion of the procedural chance ('bag squeeze'). The recommendation was amended accordingly.

Recommendations	Strength rating
In men, use a flexible cystoscope, if available and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	Strong

- 5.10.2.2 Evaluation of resection quality, resulting in a recommendation change.

Recommendations	Strength rating
Performance of individual steps	
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended if cytology or urinary molecular marker test is positive. If the equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong

- 7.2.1.3.2 Device-assisted intravesical chemotherapy - *Microwave-induced hyperthermia effect (RITE)*
- New section 7.3 Chemoablation and neoadjuvant treatment was added.
- 7.6.3 Treatment of BCG unresponsive tumours, late BCG-relapsing tumours, low-grade (LG) recurrences after BCG treatment and patients with BCG intolerance, two recommendations were amended.

General recommendations	Strength rating
In patients with high-risk tumours, full-dose intravesical bacillus Calmette-Guérin (BCG) for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems connected with BCG shortage. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
In patients with very high-risk tumours offer immediate RC. Intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC.	Strong

7.8 Guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification

Recommendations	Strength rating
EAU risk group: High	
Offer intravesical full-dose BCG instillations for one to 3 years or discuss immediate radical cystectomy (RC).	Strong

- Chapter 8 – Additional information on imaging modalities and urinary markers.

2. METHODS

2.1 Data Identification

For the 2022 NMIBC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the NMIBC Guidelines was performed. Excluded from the search were basic research studies, case series, reports, and editorial comments. Only articles published in the English language, addressing adults, were included. The search was restricted to articles published between May 29th 2020 and June 3rd 2021. Databases covered by the search included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,463 unique records were identified, retrieved, and screened for relevance.

A total of 40 new references were added to the 2022 NMIBC Guidelines. A detailed search strategy is available online: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications.

For Chapters 3 through 6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis, Predicting disease recurrence and progression) the references used in this text were assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM levels of evidence was used [5].

For each recommendation within the guidelines there is an accompanying online strength rating form based on a modified GRADE methodology [6, 7]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2021 publication was peer reviewed prior to print.

2.3 Future goals

The findings of the ongoing 'Individual Patient Data Validation of the Definition of bacillus Calmette-Guérin (BCG) Failure/BCG Unresponsive in Patients with Non-muscle Invasive Urothelial Carcinoma of the Bladder: an international multicentre retrospective study' will be included in the future update of the NMIBC Guidelines.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to tenth when both genders are considered [9]. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women [9]. In the European Union the age-standardised incidence rate is 20 for men and 4.6 for women [9].

Worldwide, the BC age-standardised mortality rate (per 100,000 person/years) was 3.3 for men vs. 0.86 for women [9]. Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and availability of treatments. The variations are, however, partly caused by the different methodologies used and the quality of data collection [10]. The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative agents [11].

Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40 years of age) this percentage is even higher [12]. Patients with TaT1 and CIS have a high prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to T2-4 tumours [9, 10].

3.2 Aetiology

Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases [10, 11, 13-15] (LE: 3). The risk of BC increases with smoking duration and smoking intensity [14]. Low-tar cigarettes are not associated with a lower risk of developing BC [14]. The risk associated with electronic cigarettes is not adequately assessed; however, carcinogens have been identified in urine [16]. Environmental exposure to tobacco smoke is also associated with an increased risk of BC [10]. Tobacco smoke contains aromatic amines and polycyclic aromatic hydrocarbons, which are renally excreted.

Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons is the second most important risk factor for BC, accounting for about 10% of all cases. This type of occupational exposure occurs mainly in industrial plants which process paint, dye, metal, and petroleum products [10, 11, 17, 18]. In developed industrial settings these risks have been reduced by work-safety guidelines; therefore, chemical workers no longer have a higher incidence of BC compared to the general population [10, 17, 18]. Recently, greater occupational exposure to diesel exhaust has been suggested as a significant risk factor (odds ratio [OR]: 1.61; 95% confidence interval [CI]: 1.08–2.40) [19].

While family history seems to have little impact [20] and, to date, no overt significance of any genetic variation for BC has been shown; genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors [10, 21-25]. This has been suggested to lead to familial clustering of BC with an increased risk for first- and second-degree relatives (hazard ratio [HR]: 1.69; 95% CI: 1.47–1.95) [26].

Although the impact of drinking habits is uncertain, the chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic, also exposure to arsenic in drinking water

increases risk [10, 27] (LE: 3). Arsenic intake and smoking have a combined effect [28]. The association between personal hair dye use and risk remains uncertain; an increased risk has been suggested in users of permanent hair dyes with a slow NAT2 acetylation phenotype [10] but a large prospective cohort study could not identify an association between hair dye and risk of most cancer and cancer-related mortality [29]. Dietary habits seem to have limited impact, recently protective impact of flavonoids has been suggested and a Mediterranean diet, characterised by a high consumption of vegetables and non-saturated fat (olive oil) and moderate consumption of protein, was linked to some reduction of BC risk (HR: 0.85, 95% CI: 0.77–0.93) [30-35]. The impact of an increased consumption of fruits has been suggested to reduce the risk of BC; to date, this effect has been demonstrated to be significant in women only (HR: 0.92; 95% CI: 0.85–0.99) [36].

Exposure to ionizing radiation is connected with increased risk; a weak association was also suggested for cyclophosphamide and pioglitazone [10, 27, 37] (LE: 3). The impact of metabolic factors (body mass index, blood pressure, plasma glucose, cholesterol, and triglycerides) is uncertain [38]. Schistosomiasis, a chronic endemic cystitis based on recurrent infection with a parasitic trematode, is also a cause of BC [10] (LE: 3).

3.3 Pathology

The information presented in this text is limited to urothelial carcinoma, unless otherwise specified.

3.4 Summary of evidence for epidemiology, aetiology, and pathology

Summary of evidence	LE
Worldwide, bladder cancer (BC) is the tenth most commonly diagnosed cancer.	2a
Several risk factors connected with the risk of BC diagnosis have been identified.	3
Tobacco smoking is the most important risk factor for BC.	3

4. PATHOLOGICAL STAGING AND CLASSIFICATION SYSTEMS

4.1 Definition of non-muscle-invasive bladder cancer

Tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively, according to the Tumour, Node, Metastasis (TNM) classification system [39]. Intra-epithelial, high-grade (HG) tumours confined to the mucosa are classified as CIS (Tis). All of these tumours can be treated by transurethral resection of the bladder (TURB), eventually in combination with intravesical instillations and are therefore grouped under the heading of NMIBC for therapeutic purposes. The term 'Non-muscle-invasive BC' represents a group definition and all tumours should be characterised according to their stage, grade, and further pathological characteristics (see Sections 4.5 and 4.7 and the International Collaboration on Cancer Reporting website: http://www.iccr-cancer.org/datasets/published-datasets/urinary-male-genital/bladder. The term 'superficial BC' should no longer be used as it is incorrect.

4.2 Tumour, Node, Metastasis Classification (TNM)

The latest TNM classification approved by the Union International Contre le Cancer (UICC) (8th Edn.) is referred to (Table 4.1) [39].

Table 4.1: 2017 TNM classification of urinary bladder cancer

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)

T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

4.3 T1 subclassification

The depth and extent of invasion into the lamina propria (T1 sub-staging) has been demonstrated to be of prognostic value in retrospective cohort studies [40, 41] (LE: 3). Its use is recommended by the most recent 2016 World Health Organization (WHO) classification [42]. T1 sub-staging methods are based either on micrometric (T1e and T1m) or histo-anatomic (T1a and T1b) principles; the optimal classification system, however, remains to be defined [42, 43].

4.4 Carcinoma *in situ* and its classification

Carcinoma *in situ* is a flat, HG, non-invasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. Carcinoma *in situ* is often multifocal and can occur in the bladder, but also in the upper urinary tract (UUT), prostatic ducts, and prostatic urethra [44].

From a clinical point of view, CIS may be classified as [45]:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

4.5 Histological grading of non-muscle-invasive bladder urothelial carcinomas

4.5.1 Types of histological grading systems

In 2004 the WHO published a histological classification system for urothelial carcinomas including papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive papillary carcinoma low grade (LG) and HG. This system was also taken into the updated 2016 WHO classification and will be maintained in the upcoming WHO 2022. It provides a different patient stratification between individual categories compared to the older 1973 WHO classification, which distinguished between grade 1 (G1), grade 2 (G2) and grade 3 (G3) categories [42, 46].

There is a significant shift of patients between the categories of the WHO 1973 and the WHO 2004/2016 systems (see Figure 4.1), for example an increase in the number of HG patients (WHO 2004/2016) due to inclusion of a subset of G2 patients with a favourable prognosis compared to the G3 category (WHO 1973) [47]. According to a multi-institutional individual patient data (IPD) analysis, the proportion of tumours classified as PUNLMP (WHO 2004/2016) has decreased to very low levels in the last decade [48].

4.5.2 Prognostic value of histological grading

A systematic review and meta-analysis did not show that the 2004/2016 classification outperforms the 1973 classification in prediction of recurrence and progression [47] (LE: 2a).

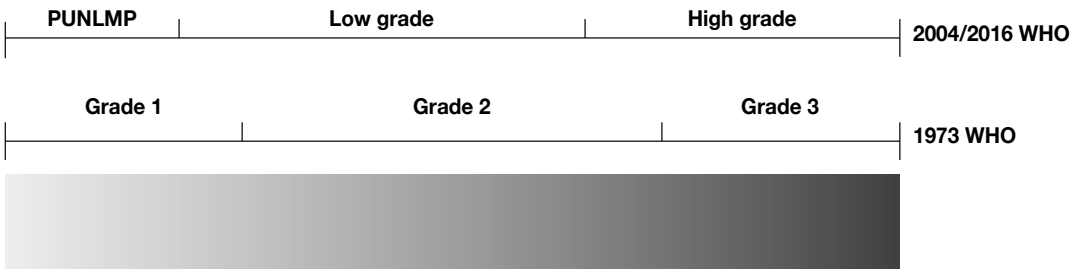
To compare the prognostic value of both WHO classifications, an IPD analysis of 5,145 primary TaT1 NMIBC patients from 17 centres throughout Europe and Canada was conducted. Patients had a transurethral resection of bladder tumour (TURBT) followed by intravesical instillations at the physician's discretion. In this large prognostic factor study, the WHO 1973 and the WHO 2004/2016 were both prognostic for progression but not for recurrence. When compared, the WHO 1973 was a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 4-tier combination LG/G1, LG/G2, HG/G2 and HG/G3) of both classification systems proved to be superior to either classification system alone, as it divides the large group of G2 patients into two subgroups (LG/HG) with different prognoses [49].

In a subgroup of 3,311 patients with primary Ta bladder tumours, a similar prognosis was found for PUNLMP and Ta LG carcinomas [50]. Hence, these results do not support the continued use of PUNLMP as a separate grade category in the WHO 2004/2016.

4.5.3 Clinical application of histological grading systems

- The WHO 2016 classification system is currently supported by the WHO for clinical application, nevertheless, the WHO 1973 is still being used by some pathologists.
- The most important parameters, which must be considered for clinical application of any grading system are its inter-observer reproducibility and prognostic value (see Sections 4.5.1 and 4.6).
- To facilitate the clinical utilisation in daily practice, these guidelines provide recommendations for tumours classified by both classification systems.

Figure 4.1: Stratification of tumours according to grade in the WHO 1973 and 2004/2016 classifications [51]*



**1973 WHO G1 carcinomas have been reassigned to papillary urothelial neoplasm of low malignant potential (PUNLMP) and LG carcinomas in the 2004/2016 WHO classification, and G2 carcinomas to LG and HG carcinomas. All 1973 WHO G3 carcinomas have been reassigned to HG carcinomas.*
PUNLMP is a non-invasive neoplasm and therefore considered stage pTa in the AJCC/UICC staging systems (Figure reproduced with permission from Elsevier).

4.6 Inter- and intra-observer variability in staging and grading

There is significant variability among pathologists for the diagnosis of CIS, for which agreement is achieved in only 70–78% of cases [52] (LE: 2a). There is also inter-observer variability in the classification of stage T1 vs. Ta tumours and tumour grading in both the 1973 and 2004/2016 classifications. The general conformity between pathologists in staging and grading is 50–60% [53-56] (LE: 2a). The WHO 2004/2016 classification provides slightly better reproducibility than the 1973 classification [47].

4.7 Subtypes of urothelial carcinoma and lymphovascular invasion

Currently the following differentiations of urothelial carcinoma are used [57, 58]:

1. urothelial carcinoma (more than 90% of all cases);
2. urothelial carcinomas with partial squamous and/or glandular or trophoblastic differentiation;
3. micropapillary urothelial carcinoma;
4. nested variant (including large nested variant) and microcystic urothelial carcinoma;
5. plasmacytoid, giant cell, signet ring, diffuse, undifferentiated;
6. lymphoepithelioma-like;
7. small-cell carcinomas;
8. sarcomatoid urothelial carcinoma;
9. neuroendocrine variant of urothelial carcinoma;
10. some urothelial carcinomas with other rare differentiations.

Most variants of urothelial carcinoma have a worse prognosis than pure HG urothelial carcinoma [2, 59-66] (LE: 3).

The presence of lymphovascular invasion (LVI) in TURB specimens is associated with an increased risk of pathological upstaging and worse prognosis [67-71] (LE: 3).

4.8 Tumour markers and molecular classification

Tumour markers and their prognostic role have been investigated [72-76]. These methods, in particular complex approaches such as the stratification of patients based on molecular classification, are promising but are not yet suitable for routine application [43, 77, 78].

4.9 Summary of evidence and guidelines for bladder cancer classification

Summary of evidence	LE
The depth of invasion (staging) is classified according to the TNM classification.	2a
Tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis).	2a
Histological grading of urothelial NMIBC is classified according to the WHO 1973 (G1–G3) and/or the WHO 2004/2016 (PUNLMP, LG/HG) systems.	2a
Both the WHO 1973 and the 2004/2016 classification systems are prognostic for progression, but not for recurrence.	2a
The WHO 1973 is a stronger prognosticator of progression in TaT1 NMIBC than the WHO 2004/2016. However, a 4-tier combination (LG/G1, LG/G2, HG/G2 and HG/G3) of both classification systems proved to be superior to either classification system alone.	2a
The WHO 2004/2016 classification provides better reproducibility than the 1973 classification.	2a
PUNLMP lesions have the same prognosis as Ta LG carcinomas.	2a

Recommendations	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO classification systems.	Weak
Do not use the term ‘superficial’ bladder cancer.	Strong

5. DIAGNOSIS

5.1 Patient history

A focused patient history is mandatory.

5.2 Signs and symptoms

Haematuria is the most common finding in NMIBC. Visible haematuria was found to be associated with higher-stage disease compared to nonvisible haematuria [79]. Carcinoma *in situ* might be suspected in patients with lower urinary tract symptoms, especially irritative voiding symptoms.

5.3 Physical examination

A focused urological examination is mandatory although it does not reveal NMIBC.

5.4 Imaging

*5.4.1 **Computed tomography urography and intravenous urography***

Computed tomography (CT) urography is used to detect papillary tumours in the urinary tract, indicated by filling defects and/or hydronephrosis [80].

Intravenous urography (IVU) is an alternative if CT is not available [81] (LE: 2b), but particularly in muscle-invasive tumours of the bladder and in UTUCs, CT urography provides more information (including status of lymph nodes and neighbouring organs).

The necessity to perform a baseline CT urography once a bladder tumour has been detected is questionable due to the low incidence of significant findings which can be obtained [82-84] (LE: 2b). The incidence of UTUCs is low (1.8%), but increases to 7.5% in tumours located in the trigone [83] (LE: 2b). The risk of UTUC during follow-up increases in patients with multiple and high-risk tumours [85] (LE: 2b).

*5.4.2 **Ultrasound***

Ultrasound (US) may be performed as an adjunct to physical examination as it has moderate sensitivity to a wide range of abnormalities in the upper- and lower urinary tract. It permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder, but cannot rule out all potential causes of haematuria [86, 87] (LE: 3). It cannot reliably exclude the presence of UTUC and cannot replace CT urography.

5.4.3 *Multi-parametric magnetic resonance imaging*

The role of multi-parametric magnetic resonance imaging (mpMRI) has not yet been established in BC diagnosis and staging. A standardised methodology of MRI reporting (Vesical Imaging-Reporting and Data System [VI-RADS]) in patients with BC has recently been published and requires further validation [88]. A first systematic review of 8 studies showed that the VI-RADS scoring system can accurately differentiate NMIBC from MIBC with high inter-observer agreement rates [89].

A diagnosis of CIS cannot be made with imaging methods alone (CT urography, IVU, US or MRI) (LE: 4).

5.5 Urinary cytology

The examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in HG and G3 tumours (84%), but low sensitivity in LG/G1 tumours (16%) [90]. The sensitivity in CIS detection is 28–100% [91] (LE: 1b). Cytology is useful, particularly as an adjunct to cystoscopy, in patients with HG/G3 tumours. Positive voided urinary cytology can indicate an urothelial carcinoma anywhere in the urinary tract; negative cytology, however, does not exclude its presence.

Cytological interpretation is user-dependent [92, 93]. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations, however, in experienced hands specificity exceeds 90% [92] (LE: 2b).

A standardised reporting system known as The Paris System published in 2016 redefined urinary cytology diagnostic categories as follows [94]:

- No adequate diagnosis possible (No diagnosis);
- Negative for urothelial carcinoma (Negative);
- Atypical urothelial cells (Atypia);
- Suspicious for HG urothelial carcinoma (Suspicious);
- High-grade/G3 urothelial carcinoma (Malignant).

The principle of the system and its terminology underlines the role of urinary cytology in detection of G3 and HG tumours. The Paris system for reporting urinary cytology has been validated in several retrospective studies [95, 96].

Urine collection should respect the recommendation provided in Section 5.9. One cytospin slide from the sample is usually sufficient [97]. In patients with suspicious cytology repeat investigation is advised [98] (LE: 2b).

5.6 Urinary molecular marker tests

Driven by the low sensitivity of urine cytology, numerous urinary tests have been developed [99]. None of these markers have been accepted as routine practice by any clinical guidelines for diagnosis or follow-up.

The following conclusions can be drawn regarding the existing tests:

- Sensitivity is usually higher at the cost of lower specificity compared to urine cytology [100-105] (LE: 3).
- Benign conditions and previous BCG instillations may influence the results of many urinary marker tests [100-102] (LE: 1b).
- Requirements for sensitivity and specificity of a urinary marker test largely depend on the clinical context of the patient (screening, primary detection, follow-up [high-risk, low/intermediate-risk]) [101, 102] (LE: 3).
- The wide range in performance of the markers and low reproducibility may be explained by patient selection and complicated laboratory methods required [102, 103, 106-113].
- Positive results of cytology, UroVysion (FISH), Nuclear Matrix Protein (NMP)22®, *Fibroblast Growth Factor Receptor (FGFR)3/Telomerase Reverse Transcriptase (TERT)* and microsatellite analysis in patients with negative cystoscopy and upper tract work-up, may identify patients more likely to experience disease recurrence and possibly progression [107, 109, 112-117] (LE: 2b).
- Promising novel urinary biomarkers, assessing multiple targets, have been tested in prospective multicentre studies [106, 108, 112, 118-121].

5.7 Potential application of urinary cytology and markers

The following objectives of urinary cytology or molecular tests must be considered.

5.7.1 *Screening of the population at risk of bladder cancer*

The application of haematuria dipstick, followed by *FGFR3*, NMP22® or UroVysion tests if dipstick is positive has been reported in BC screening in high-risk populations [122, 123]. The low incidence of BC in the general population and the short lead-time impair feasibility and cost-effectiveness [115, 123]. Routine screening for BC is not recommended [115, 122, 123].

*5.7.2 **Exploration of patients after haematuria or other symptoms suggestive of bladder cancer (primary detection)***

It is generally accepted that none of the currently available tests can replace cystoscopy. However, urinary cytology or biomarkers can be used as an adjunct to cystoscopy to detect missed tumours, particularly CIS. In this setting, specificity is particularly important.

*5.7.3 **Surveillance of non-muscle-invasive bladder cancer***

Research has been carried out into the usefulness of urinary cytology vs. markers in the follow-up of NMIBC [106, 107, 119, 120, 124].

5.7.3.1 Follow-up of high-risk non-muscle-invasive bladder cancer

High-risk tumours should be detected early in follow-up and the percentage of tumours missed should be as low as possible. Therefore, the best surveillance strategy for these patients will continue to include cystoscopy and cytology (see Chapter 8).

5.7.3.2 Follow-up of low/intermediate-risk non-muscle-invasive bladder cancer

To reduce the number of cystoscopy procedures, urinary markers should be able to detect recurrence before the tumours are large, numerous and muscle invasive. The limitation of urinary cytology and current urinary markers is their low sensitivity for LG recurrences [101, 107] (LE: 1b).

According to current knowledge, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion. One prospective randomised study (RCT) found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [125] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed prior to follow-up cystoscopy [125] (see Section 8.1).

Four of the promising and commercially available urine biomarkers, Cx-Bladder [106, 121], ADX-Bladder [118], Xpert Bladder [119] and EpiCheck [120], although not tested in RCTs, have such high sensitivities and negative predictive values in the referenced studies for HG disease that these biomarkers may approach the sensitivity of cystoscopy. These 4 tests might be used to replace and/or postpone cystoscopy as they may identify the rare HG recurrences occurring in low/intermediate NMIBC.

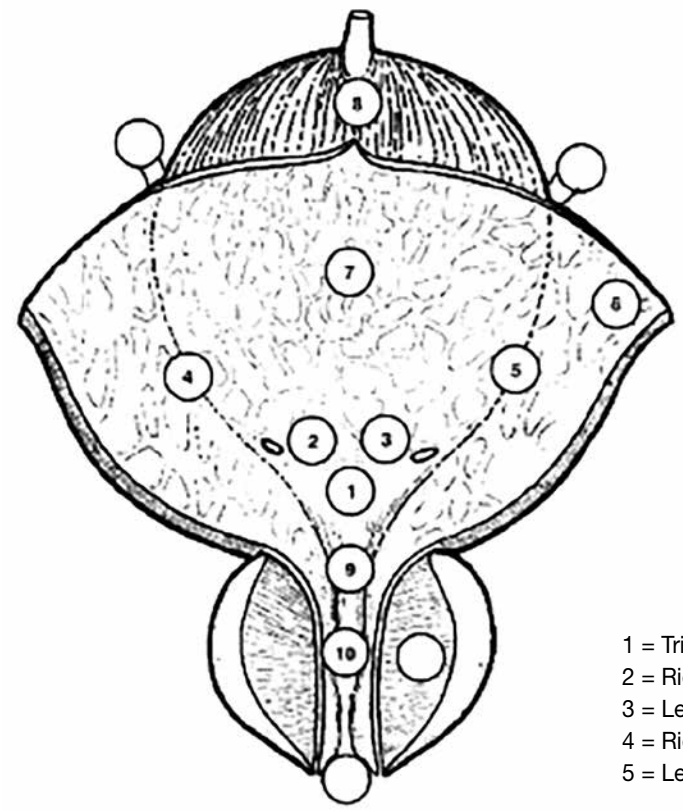
5.8 Cystoscopy

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of sampled tissue by either cold-cup biopsy or resection. Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of multiple bladder biopsies [126].

Cystoscopy is initially performed as an outpatient procedure. A flexible instrument with topical intraurethral anaesthetic lubricant instillation results in better compliance compared to a rigid instrument, especially in men [127, 128] (LE: 1b).

To temporary increase the urethral pressure by irrigation ‘bag squeeze’ when passing membranous and prostatic urethra with a flexible cystoscope in males also decreases pain during the procedure [129, 130].

Figure 5.1: Bladder diagram



1 = Trigone
2 = Right ureteral orifice
3 = Left ureteral orifice
4 = Right wall
5 = Left wall
6 = Anterior wall
7 = Posterior wall
8 = Dome
9 = Neck
10 = Posterior urethra

5.9 Summary of evidence and guidelines for the primary assessment of non-muscle-invasive bladder cancer

Summary of evidence	LE
Cystoscopy is necessary for the diagnosis of BC.	1
Urinary cytology has high sensitivity in high-grade tumours including carcinoma *in situ*	2b

Recommendations	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography-intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	Strong
Describe all macroscopic features of the tumour (site, size, number, and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram (Figure 5.1).	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong
Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris System for cytology reporting.	Strong

5.10 Transurethral resection of TaT1 bladder tumours

*5.10.1 **Strategy of the procedure***

The goal of TURB in TaT1 BC is to make the correct diagnosis and completely remove all visible lesions. It is a crucial procedure in the management of BC. Transurethral resection of the bladder should be performed systematically in individual steps [131, 132] (see Section 5.14).

The operative steps necessary to achieve a successful TURB include identifying the factors required to

assign disease risk (number of tumours, size, multifocality, characteristics, concern for the presence of CIS, recurrent vs. primary tumour), clinical stage (bimanual examination under anaesthesia, assignment of clinical tumour stage), adequacy of the resection (visually complete resection, visualisation of muscle at the resection base), and presence of complications (assessment for perforation) [132, 133]. To measure the size of the largest tumour, one can use the end of cutting loop, which is approximately 1 cm wide, as a reference. The characteristics of the tumour are described as sessile, nodular, papillary, or flat.

5.10.2 ***Surgical and technical aspects of tumour resection***

5.10.2.1 Surgical strategy of resection (piecemeal/separate resection, en-bloc resection)

A complete resection, performed by either fractioned or *en-bloc* technique, is essential to achieve a good prognosis [131, 134].

- Piecemeal resection in fractions (separate resection of the exophytic part of the tumour, the underlying bladder wall and the edges of the resection area) provides good information about the vertical and horizontal extent of the tumour [135] (LE: 2b).
- *En-bloc* resection using monopolar or bipolar current, Thulium-YAG or Holmium-YAG laser is feasible in selected exophytic tumours. It provides high-quality resected specimens with the presence of detrusor muscle in 96–100% of cases [131, 136-139] (LE: 1b).

The technique selected is dependent on the size and location of the tumour and experience of the surgeon.

5.10.2.2 Evaluation of resection quality

The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease, early recurrence, and tumour under-staging [140] (LE: 1b). The presence of detrusor muscle in the specimen is considered as a surrogate criterion of the resection quality and is required (except in Ta LG/G1 tumours). Surgical checklists and a quality performance indicator programmes have shown to increase surgical quality (detrusor muscle presence) and decrease recurrence rates [132, 133, 141, 142].

It has been shown that surgical experience can improve TURB results, which supports the role of teaching programmes [143]. Virtual training on simulators is an emerging approach [144]. Its role in the teaching process still needs to be established [132]. Surgical experience and/or volume has been associated both with risk of complications [145], recurrence [146] and survival [147] in retrospective studies (LE: 3).

5.10.2.3 Monopolar and bipolar resection

Compared to monopolar resection, bipolar resection has been introduced to reduce the risk of complications (e.g., bladder perforation due to obturator nerve stimulation) and to produce better specimens. Currently, the results remain controversial [148-151] as a systematic review of 13 RCTs (2,379 patients) showed no benefit of bipolar vs. monopolar TURB for efficacy and safety [151].

5.10.2.4 Office-based fulguration and laser vaporisation

In patients with a history of small, Ta LG/G1 tumours, fulguration, or laser vaporisation of small papillary recurrences on an outpatient basis can reduce the therapeutic burden [152, 153] (LE: 3). There are no prospective comparative studies assessing the oncological outcomes.

5.10.2.5 Resection of small papillary bladder tumours at the time of transurethral resection of the prostate

It is not uncommon to detect bladder tumours in men with benign prostatic hyperplasia. Provided these tumours are papillary by aspect, rather small and not extensively multifocal, it seems feasible to resect these tumours and continue with the resection of the prostate [154, 155]. Although high-quality evidence is limited, simultaneous TURB and TUR of the prostate does not appear to lead to any increased risk of tumour recurrence or progression [156].

5.10.3 ***Bladder biopsies***

Carcinoma *in situ* can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all. For this reason, biopsies from suspicious urothelium should be taken. In patients with positive urine cytology (see Section 5.5), and normal-looking mucosa at cystoscopy, mapping biopsies are recommended [157, 158]. To obtain representative mapping of the bladder mucosa, biopsies should be taken from the trigone, bladder dome, right, left, anterior and posterior bladder wall [157, 158]. If the equipment is available, photodynamic diagnosis (PDD) is a useful tool to target the biopsy.

5.10.4 ***Prostatic urethral biopsies***

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported. Palou *et al*. showed that in 128 men with T1G3 BC, the incidence of CIS in the prostatic urethra was 11.7% [159] (LE: 2b). The risk

of prostatic urethra or duct involvement is higher if the tumour is located at the trigone or bladder neck, in the presence of bladder CIS and multiple tumours [160] (LE: 3b). Based on this observation, a biopsy from the prostatic urethra is necessary in some cases (see recommendation in Section 5.14) [159, 161, 162].

5.11 New methods of tumour visualisation

As a standard procedure, cystoscopy and TURB are performed using white light. However, the use of white light can lead to missing lesions that are present but not visible, which is why new technologies are being developed.

5.11.1 Photodynamic diagnosis (fluorescence cystoscopy)

Photodynamic diagnosis is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexaminolaevulinic acid (HAL). It has been confirmed that fluorescence-guided biopsy and resection are more sensitive than conventional procedures for the detection of malignant tumours, particularly CIS [163, 164] (LE: 1a). In a systematic review and meta-analysis, PDD had higher sensitivity than white light endoscopy in the pooled estimates for analyses at both the patient-level (92% vs. 71%) and biopsy-level (93% vs. 65%) [164]. A prospective RCT did not confirm a higher detection rate in patients with known positive cytology before TURB [165].

Photodynamic diagnosis had lower specificity than white-light endoscopy (63% vs. 81%) [164]. False-positivity can be induced by inflammation or recent TURB and during the first 3 months after BCG instillation [166, 167] (LE: 1a).

The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURB was evaluated. A systematic review and analysis of 14 RCTs including 2,906 patients, 6 using 5-ALA and 9 HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [168] (LE: 1a).

One RCT has shown a reduction in recurrence and progression with fluorescence-guided TURB as compared to white light TURB [169]. In another RCT flexible HAL-cystoscopy proved beneficial in the outpatient setting showing subsequent lower recurrence rates [170]. These results need to be validated by further studies.

5.11.2 Narrow-band imaging

In narrow-band imaging (NBI), the contrast between normal urothelium and hyper-vascular cancer tissue is enhanced. Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection [171-174] (LE: 3b). A RCT assessed the reduction of recurrence rates if NBI is used during TURB. Although the overall results of the study were negative, a benefit after 3 and 12 months was observed for low-risk tumours (pTa LG, < 30 mm, no CIS) [175] (LE: 1b).

5.11.3 Additional technologies

Confocal laser micro-endoscopy is a high resolution imaging probe designed to provide endoscopic histological grading in real time but requires further validation [176]. The Storz professional image enhancement system (IMAGE1 S, formally called SPIES) is an image enhancement system using 4 different light spectra but prospective data using this system are still limited [177].

5.12 Second resection

5.12.1 Detection of residual disease and tumour upstaging

The significant risk of residual tumour after initial TURB of TaT1 lesions has been demonstrated [134] (LE: 1b).

A systematic review analysing data of 8,409 patients with Ta or T1 HG BC demonstrated a 51% risk of persistence and an 8% risk of under-staging in T1 tumours. The analysis also showed a high risk of residual disease in Ta tumours, but this observation was based only on a limited number of cases. Most of the residual lesions were detected at the original tumour location [178] (LE: 1a).

Another meta-analysis of 3,556 patients with T1 tumours showed that the prevalence rate of residual tumours and upstaging to invasive disease after TURB remained high in a subgroup with detrusor muscle in the resection specimen. In the subgroup of 1,565 T1 tumours with detrusor muscle present, persistent tumour was found in 58% and under-staging occurred in 11% of cases [179].

Prospective trials suggest that post-operative positive urine cytology [180] and Xpert-test (urine mRNA test) [181] independently are associated with residual disease at second resection and risk of future recurrences, respectively (LE: 2b). These data, however, need to be confirmed in further studies.

5.12.2 The impact of second resection on treatment outcomes

A second TURB can increase recurrence-free survival (RFS) [182, 183] (LE: 2a), improve outcomes after BCG treatment [184] (LE: 3) and provide prognostic information [185-188] (LE: 3).

In a retrospective evaluation of a large multi-institutional cohort of 2,451 patients with BCG-treated T1 G3/HG tumours (a second resection was performed in 935 patients), the second resection improved RFS, progression-free survival (PFS) and overall survival (OS) only in patients without detrusor muscle in the specimen of the initial resection [189] (LE: 3).

5.12.3 Timing of second resection

Retrospective evaluation showed that a second resection performed 14–42 days after initial resection provides longer RFS and PFS compared to second resection performed after 43–90 days [190] (LE: 3). Based on these arguments, a second TURB is recommended in selected cases 2 to 6 weeks after initial resection (for recommendations on patient selection, see Section 5.14).

5.12.4 Recording of results

The results of the second resection (residual tumours and under-staging) reflect the quality of the initial TURB. As the goal is to improve the quality of the initial TURB, the results of the second resection should be recorded.

5.13 Pathology report

Pathological investigation of the specimen(s) obtained by TURB and biopsies is an essential step in the decision-making process for BC [191]. Close co-operation between urologists and pathologists is required. A high quality of resected and submitted tissue and clinical information is essential for correct pathological assessment. To obtain all relevant information, the specimen collection, handling and evaluation, should respect the recommendations provided below (see Section 5.14) [192, 193]. In difficult cases, an additional review by an experienced genitourinary pathologist can be considered.

5.14 Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report

Summary of evidence	LE
Transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) is an essential step in the management of NMIBC.	1
The absence of detrusor muscle in the specimen is associated with a significantly higher risk of residual disease and tumour under-staging (with the exception of Ta LG/G1 tumours).	2b
In patients with a history of small Ta LG/G1 tumours, fulguration of small papillary recurrences on an outpatient basis is feasible and safe.	3
A second TURB can detect residual tumours and tumour under-staging, increase recurrence-free survival, improve outcomes after BCG treatment and provide prognostic information.	2

Recommendations	Strength rating
In patients suspected of having bladder cancer, perform a transurethral resection of the bladder tumour (TURB) followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of Ta LG/G1 tumours.	Weak
Perform TURB systematically in individual steps: • bimanual palpation under anaesthesia. • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen(s) for pathology evaluation.	Strong
Performance of individual steps	
Perform *en-bloc* resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong
Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong

Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended if cytology or urinary molecular marker test is positive. If the equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma *in situ* is present or suspected, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak
The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a second TURB in the following situations: • after incomplete initial TURB, or in case of doubt about completeness of a TURB; • if there is no detrusor muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; • in T1 tumours.	Strong
If indicated, perform a second TURB within 2–6 weeks after the initial resection. This second TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a second TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, subtypes of urothelial carcinoma (variant histologies), presence of CIS and detrusor muscle.	Strong

6. PREDICTING DISEASE RECURRENCE AND PROGRESSION

6.1 TaT1 tumours

Treatment should take into account a patient's prognosis. In order to predict the risk of disease recurrence and/or progression, several prognostic models for specified patient populations have been introduced.

*6.1.1 **Scoring models using the WHO 1973 classification system***

6.1.1.1 The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model

To be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables based on the WHO 1973 classification in 2006 [194]. The scoring system is based on the 6 most significant clinical and pathological factors in patients mainly treated by intravesical chemotherapy:

- Number of tumours;
- Tumour diameter;
- Prior recurrence rate;
- T category;
- Concurrent CIS;
- WHO 1973 tumour grade.

Using the 2006 EORTC scoring model, individual probabilities of recurrence and progression at 1 and 5 years may be calculated (https://www.omnicalculator.com/health/eortc-bladder-cancer).

6.1.1.2 The model for patients with Ta G1/G2 (WHO 1973) tumours treated with chemotherapy

Patients with Ta G1/G2 tumours receiving chemotherapy were stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy [195].

6.1.1.3 Club Urologico Español de Tratamiento Oncologico (CUETO) scoring model for BCG-treated patients

A model that predicts the risk of recurrence and progression, based on 12 doses of intravesical BCG over a 5 to 6 months period following TURB, has been published by the CUETO (Spanish Urological Oncology Group). It is based on an analysis of 1,062 patients from 4 CUETO trials that compared different intravesical BCG treatments. No immediate post-operative instillation or second TURB was performed in these patients. The scoring system is based on the evaluation of seven prognostic factors:

- gender;
- age;
- prior recurrence status;
- number of tumours;
- T category;
- associated CIS;
- WHO 1973 tumour grade.

Using this model, the calculated risk of recurrence is lower than that obtained by the EORTC tables. For progression, probability is lower only in high-risk patients [196] (LE: 2a). The lower risks in the CUETO tables may be attributed to the use of BCG in this study. The prognostic value of the EORTC scoring system has been confirmed by data from the CUETO patients treated with BCG and by long-term follow-up in an independent patient population [197, 198] (LE: 2a).

6.1.1.4 The 2016 EORTC scoring model for patients treated with maintenance BCG

In 1,812 intermediate- and high-risk patients without CIS treated with 1 to 3 years of maintenance BCG, the EORTC found that the prior disease-recurrence rate and number of tumours were the most important prognostic factors for disease recurrence, stage and WHO 1973 grade for disease progression and disease-specific survival, while age and WHO 1973 grade were the most important prognostic factors for OS. T1 G3 patients did poorly, with 1- and 5-year disease-progression rates of 11.4% and 19.8%, respectively. Using these data, EORTC risk groups and nomograms for BCG-treated patients were developed [199] (LE: 2a).

*6.1.2 **Scoring model using the WHO 2004/2016 and WHO 1973 classification systems***

6.1.2.1 EAU NMIBC 2021 scoring model

To update the risk of disease progression and create new prognostic factor risk groups using both the WHO 1973 and WHO 2004/2016 classification systems (without central pathology review), individual patient data from 3,401 primary patients treated from 1990 to 2018 were used [50] (see Section 4.5). Only patients treated with TURB ± intravesical chemotherapy were included, those treated with adjuvant intravesical BCG were excluded because BCG may reduce the risk of disease progression. From the multivariate analysis, tumour stage, WHO 1973 grade, WHO 2004/2016 grade, concomitant CIS, number of tumours, tumour size and age were independent predictors of disease progression [50].

This is the only available model where the WHO 2004/2016 classification system is included as one of the parameters to calculate an individual patient's risk group and probability of progression. As the WHO 2004/2016 classification system is the main grading classification system used by pathologists, the Guidelines Panel recommends to use the 2021 EAU NMIBC scoring model for risk groups definition (see Section 6.3).

As the 2021 EAU NMIBC scoring model determines the risk of tumour progression, but not recurrence, any of models mentioned in Section 6.1.1 may be used for calculation of an individual's risk of disease recurrence.

*6.1.3 **Further prognostic factors***

Further prognostic factors have been described in selected patient populations:

- In T1G3 tumours, important prognostic factors were female sex, CIS in the prostatic urethra in men treated with an induction course of BCG, and age, tumour size and concurrent CIS in BCG-treated patients (62% with an induction course only) [159, 200] (LE: 2b).
- Attention must be given to patients with T1G3 tumours in bladder (pseudo) diverticulum because of the absence of muscle layer in the diverticular wall [201] (LE: 3).
- In patients with T1 tumours, the finding of residual T1 disease at second TURB is an unfavourable prognostic factor [186-188] (LE: 3).

- In patients with T1G2 tumours treated with TURB, recurrence at 3 months was the most important predictor of progression [202] (LE: 2b).
- The prognostic value of pathological factors has been discussed elsewhere (see Section 4.6). More research is needed to determine the role of molecular markers in improving the predictive accuracy of currently available risk tables [197, 203].
- Pre-operative neutrophil-to-lymphocyte ratio may have prognostic value in NMIBC. This data, however, needs further validation [204].

6.2 Carcinoma *in situ*

Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease [205] (LE: 3). There are no reliable prognostic factors, but some studies, however, have reported a worse prognosis in concurrent CIS and T1 tumours compared to primary CIS [206, 207], in extended CIS [208] and in CIS in the prostatic urethra [159] (LE: 3).

The response to intravesical treatment with BCG or chemotherapy is an important prognostic factor for subsequent progression and death caused by BC [196-198, 202]. Approximately 10 to 20% of complete responders eventually progress to muscle-invasive disease, compared with 66% of non-responders [209, 210] (LE: 2a).

6.3 Patient stratification into risk groups

To be able to facilitate treatment recommendations, the Guidelines Panel recommends the stratification of patients into risk groups based on their probability of progression to muscle-invasive disease. The new risk group definitions provided in these EAU Guidelines are based on an IPD analysis in primary patients and the calculation of their progression scores (2021 EAU NMIBC scoring model) as presented in Sections 4.5 and 6.1.2) [50].

For calculation of the risk group in individual patients, either one, or both, of the WHO 1973 and WHO 2004/2016 classification systems may be used. The probability of progression at 5 years varies from less than 1% to more than 40% between the risk groups.

For factors where IPD were not collected such as subtypes of urothelial carcinoma (variant histologies), LVI, primary CIS and CIS in the prostatic urethra; literature data have been used to classify patients into risk groups.

The clinical compositions of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or WHO 1973 classification systems are provided in Table 6.1. Apps for the web (www.nmibc.net), iOS and Android (iOS / https://apps.apple.com/us/app/eau-nmibc-risk-calculator/id1578482687 and Android / https://play.google.com/store/apps/details?id=net.ydeal.nmibc) have been developed to facilitate determining a patient's risk group in daily clinical practice. The individual probability of disease progression at 1, 5 and 10 years for the new EAU NMIBC risk groups is presented in Table 6.2.

Table 6.1: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems [50]

- Only one of the two classification systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both classification systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973 as it has better prognostic value.
- The category of LG tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are*:
    - o age > 70;
    - o multiple papillary tumours;
    - o tumour diameter ≥ 3 cm.

Risk group	
Low Risk	• A primary, single, TaT1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years
	• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)
Intermediate Risk	Patients without CIS who are not included in either the low-, high-, or very high-risk groups
High Risk	• All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor

Very High Risk	**Stage, grade with additional clinical risk factors:** • Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

The scoring model is based on IPD, but does not consider patients with primary CIS (high risk) or with recurrent tumours, as well as some pathologic parameters like subtypes of urothelial carcinoma (variant histologies, see Section 4.7) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with subtypes of urothelial carcinoma (see Section 4.7) or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high-, or very high-risk groups according to their other prognostic factors.

Table 6.2: Probabilities of disease progression in 1, 5 and 10 year(s) for the new EAU NMIBC risk groups [50]*

Risk group	Probability of Progression and 95% Confidence Interval (CI)		
	1 Year	5 Years	10 Years
New Risk Groups with WHO 2004/2016			
Low	0.06% (CI: 0.01%–0.43%)	0.93% (CI: 0.49%–1.7%)	3.7% (CI: 2.3%–5.9%)
Intermediate	1.0% (CI: 0.50%–2.0%)	4.9% (CI: 3.4%–7.0%)	8.5% (CI: 5.6%–13%)
High	3.5% (CI: 2.4%–5.2%)	9.6% (CI: 7.4%–12%)	14% (CI: 11%–18%)
Very High	16% (CI: 10%–26%)	40% (CI: 29%–54%)	53% (CI: 36%–73%)
New Risk Groups with WHO 1973			
Low	0.12% (CI: 0.02%–0.82%)	0.57% (CI: 0.21%–1.5%)	3.0% (CI: 1.5%–6.3%)
Intermediate	0.65% (CI: 0.36%–1.2%)	3.6% (CI: 2.7%–4.9%)	7.4% (CI: 5.5%–10%)
High	3.8% (CI: 2.6%–5.7%)	11% (CI: 8.1%–14%)	14% (CI: 10%–19%)
Very High	20% (CI: 12%–32%)	44% (CI: 30%–61%)	59% (CI: 39%–79%)

WHO = World Health Organization.

**Table 6.2 does not include patients with subtypes of urothelial carcinoma (variant histologies), LVI, CIS in the prostatic urethra, primary CIS or recurrent patients.*

6.4 Summary of evidence and guidelines for stratification of non-muscle-invasive bladder cancer

Summary of evidence	LE
The EAU NMIBC 2021 scoring model and risk tables predict the short- and long-term risks of disease progression in individual patients with primary NMIBC using either the WHO 1973 or the WHO 2004/2016 classification system (see Section 6.1.2.1).	2b
The 2006 EORTC scoring model and risk tables predict the short- and long-term risks of disease recurrence and progression in individual patients with NMIBC using the WHO 1973 classification system (see Section 6.1.1.1).	1b
Patients with Ta G1/G2 tumours receiving chemotherapy have been further stratified into 3 risk groups for recurrence, taking into account the history of recurrences, history of intravesical treatment, tumour grade (WHO 1973), number of tumours and adjuvant chemotherapy (see Section 6.1.1.2).	2b
In patients treated with 5 to 6 months of BCG, the CUETO scoring model predicts the short- and long-term risks of disease recurrence and progression using the WHO 1973 classification system (see Section 6.1.1.3).	1b
In patients receiving at least 1 year of BCG maintenance; prior recurrence rate and number of tumours are the most important prognostic factors for disease recurrence. Stage and grade are the most important prognostic factors for disease progression and disease-specific survival; patient age and grade (WHO 1973) are the most important prognostic factors for OS (see Section 6.1.1.4).	1b

Recommendations	Strength rating
Stratify patients into 4 risk groups according to Table 6.1. A patient's risk group can be determined using the EAU risk group calculator available at www.nmibc.net.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours not treated with BCG, use the data from Table 6.2.	Strong

Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with bacillus Calmette-Guérin (BCG).	Strong
Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1 to 3 years of maintenance, the CUETO model for 5 to 6 months of BCG).	Strong

7. DISEASE MANAGEMENT

7.1 Counselling of smoking cessation

It has been confirmed that smoking increases the risk of tumour recurrence and progression [211, 212] (LE: 3). While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counselled to stop smoking due to the general risks connected with tobacco smoking [201, 213-215] (LE: 3).

7.2 Adjuvant treatment

Although TURB by itself can eradicate a TaT1 tumour completely, these tumours commonly recur and can progress to MIBC. The high variability in the 3-month recurrence rate indicates that the TURB was incomplete or provokes recurrences in a high percentage of patients [134]. It is therefore necessary to consider adjuvant therapy in all patients.

7.2.1 Intravesical chemotherapy

7.2.1.1 A single, immediate, post-operative intravesical instillation of chemotherapy

Immediate single instillation (SI) has been shown to act by destroying circulating tumour cells after TURB, and by an ablative effect on residual tumour cells at the resection site and on small overlooked tumours [216-219] (LE: 3).

Four large meta-analyses comprising 1,476 to 3,103 patients have consistently shown that after TURB, SI significantly reduces the recurrence rate compared to TURB alone [220-223] (LE: 1a). In a systematic review and IPD meta-analysis of 2,278 eligible patients [220], SI reduced the 5-year recurrence rate by 14%, from 59% to 45%. Only patients with primary tumours or intermediate-risk recurrent tumours with a prior recurrence rate of ≤ 1 recurrence/year and those with a 2006 EORTC recurrence score < 5 benefited from SI. In patients with a 2006 EORTC recurrence score ≥ 5 and/or patients with a prior recurrence rate of > 1 recurrence per year, SI was not effective as a single adjuvant treatment. No randomised comparisons of individual drugs have been conducted [220-223].

Single instillation with mitomycin C (MMC), epirubicin or pirarubicin, have all shown a beneficial effect [220]. Single instillation with gemcitabine was superior to placebo control (saline) in a RCT with approximately 200 patients per arm with remarkably low toxicity rates [224]. These findings are in contrast with a previous study, which, however, used a shorter instillation time [225]. In the Böhle *et al.* study, continuous saline irrigation was used for 24 hours post-operatively in both arms, which could explain the low recurrence rate in the control arm [225]. Two meta-analyses suggest efficacy of continuous saline irrigation in the prevention of early recurrences [226, 227].

Prevention of tumour cell implantation should be initiated within the first few hours after TURB. After that, tumour cells are firmly implanted and are covered by the extracellular matrix [216, 228-230] (LE: 3). In all SI studies, the instillation was administered within 24 hours. Two RCTs found no overall impact of SI with apaziquone; in contrast, a post-hoc analysis did find a reduction of recurrence risk in patients receiving apaziquone within 90 minutes following TURB [231]. To maximise the efficacy of SI, one should devise flexible practices that allow the instillation to be given as soon as possible after TURB, preferably within the first two hours in the recovery room or even in the operating theatre. As severe complications have been reported in patients with drug extravasation [232, 233] safety measures should be maintained (see Section 7.7).

7.2.1.2 Additional adjuvant intravesical chemotherapy instillations

The need for further adjuvant intravesical therapy depends on prognosis. In low-risk patients (Tables 6.1 and 6.2), a SI reduces the risk of recurrence and is considered to be the standard and complete treatment [220, 221] (LE: 1a). For other patients, however, a SI remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression (Tables 6.1 and 6.2). Efficacy data for the following comparisons of application schemes were published:

Single installation only vs. SI and further repeat instillations
In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [234] (LE: 2a).

Repeat chemotherapy instillations vs. no adjuvant treatment
A large meta-analysis of 3,703 patients from 11 RCTs showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [235]. This corresponds to an absolute difference of 13–14% in the number of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [236, 237] (see Section 7.2.2.1) (LE: 1a). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [238-240] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [240] (LE: 1a).

Single instillation + further repeat instillations vs. later repeat instillations only
There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given [241-244]. A RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at 3 years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [241] (LE: 2a). Since the author's definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [245]. The results of this study should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC [246].

The optimal schedule of intravesical chemotherapy instillations
The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [244] (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy
7.2.1.3.1 Adjustment of pH, duration of instillation, and drug concentration
A prospective randomised, multi-institutional RCT showed that intravesical solution reduced the recurrence rate [247] (LE: 1b). Another trial reported that duration of a one hour instillation of MMC was more effective compared to a 30-minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [248] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [249] (LE: 1b). In view of these data, instructions are provided (see Section 7.7).

It has been suggested that the efficacy of MMC may be improved by optimising application through the adjustment of urine pH, in addition to the use of alternative maintenance schedules. Neither aspect is reflected in the literature quoted above since most published studies do not support this approach.

7.2.1.3.2 Device-assisted intravesical chemotherapy
Microwave-induced hyperthermia effect (RITE)
Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [250]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [251] (LE: 1b).

Hyperthermic intravesical chemotherapy
Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration
The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [252]. The definitive conclusion, however, needs further confirmation.

For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.6.3.

7.2.1.4 Summary of evidence - intravesical chemotherapy

Summary of evidence	LE
In patients with low-risk NMIBC and in those with a small Ta LG/G1 recurrence detected more than one year after previous TURB, a SI significantly reduces the recurrence rate compared to TURB alone.	1a
Single instillation might have an impact on recurrence even when further adjuvant chemotherapy instillations are given.	3
Repeat chemotherapy instillations (with or without previous SI) improve RFS in intermediate-risk patients.	2a

7.2.2 ***Intravesical bacillus Calmette-Guérin (BCG) immunotherapy***

7.2.2.1 Efficacy of BCG

7.2.2.1.1 Recurrence rate

Five meta-analyses have confirmed that BCG after TURB is superior to TURB alone or TURB plus chemotherapy for preventing the recurrence of NMIBC [238, 253-256] (LE: 1a). Three RCTs of intermediate- and high-risk tumours have compared BCG with epirubicin and interferon (INF) [257], MMC [258], or epirubicin alone [239] and have confirmed the superiority of BCG for prevention of tumour recurrence (LE: 1a). The effect is long lasting [239, 258] and was also observed in a separate analysis of patients with intermediate-risk tumours [239]. One meta-analysis [238] has evaluated the individual data from 2,820 patients enrolled in 9 RCTs that have compared MMC vs. BCG. In the trials with BCG maintenance, there was a 32% reduction in the risk of recurrence for BCG compared to MMC, but a 28% increase in the risk of recurrence for patients treated with BCG in the trials without BCG maintenance. A Cochrane systematic review confirmed that BCG is more effective in reducing the recurrence rate over MMC [259].

7.2.2.1.2 Progression rate

Two meta-analyses have demonstrated that BCG therapy delays and potentially lowers the risk of tumour progression [236, 237, 256] (LE: 1a). A meta-analysis carried out by the EORTC Genito-Urinary Cancers Group (GUCG) has evaluated data from 4,863 patients enrolled in 24 RCTs. In 20 of the trials, some form of BCG maintenance was used. Based on a median follow-up of 2.5 years, tumours progressed in 9.8% of the patients treated with BCG compared to 13.8% in the control groups (TURB alone, TURB and intravesical chemotherapy, or TURB with the addition of other immunotherapy). This shows a reduction of 27% in the odds of progression with BCG maintenance treatment. The size of the reduction was similar in patients with TaT1 papillary tumours and in those with CIS [237]. A RCT with long-term follow-up has demonstrated significantly fewer distant metastases and better overall- and disease-specific survival in patients treated with BCG compared to epirubicin [239] (LE: 1b). In contrast, an IPD meta-analysis and Cochrane review were not able to confirm any statistically significant difference between MMC and BCG for progression, survival, and cause of death [238, 259].

The conflicting results in the outcomes of these studies can be explained by different patient characteristics, duration of follow-up, methodology and statistical power. However, most studies showed a reduction in the risk of progression in high-and intermediate-risk tumours if a BCG maintenance schedule was applied.

7.2.2.1.3 Influence of further factors

Two other meta-analyses have suggested a possible bias in favour of BCG arising from the inclusion of patients previously treated with intravesical chemotherapy [260]. In the IPD meta-analysis, however, BCG maintenance was more effective than MMC in reduction of recurrence rate, both in patients previously treated and not previously treated with chemotherapy [238] (LE: 1a). It was demonstrated that BCG was less effective in patients > 70 years of age, but still more effective than epirubicin in a cohort of elderly patients [261] (LE: 1a). According to a cohort analysis, the risk of tumour recurrence after BCG was shown to be higher in patients with a previous history of UTUC [262].

7.2.2.2 BCG strain

Although smaller studies without maintenance demonstrated some differences between strains [262-264], a network meta-analysis identified ten different BCG strains used for intravesical treatment in the published literature but was not able to confirm superiority of any BCG strain over another [265].

Similarly, a published meta-analysis of prospective RCTs [237], published data from a prospective registry [266] as well as from a *post-hoc* analysis of a large phase II prospective trial assessing BCG and INF-α in both BCG-naive and BCG-failure patients did not suggest any clear difference in efficacy between the different BCG strains [267] (LE: 2a). The quality of data, however, does not allow definitive conclusions.

7.2.2.3 BCG toxicity

Bacillus Calmette-Guérin intravesical treatment is associated with more side effects compared to intravesical chemotherapy [237, 259] (LE: 1a). However, serious side effects are encountered in < 5% of patients and can be treated effectively in almost all cases [268] (LE: 1b). The incidence of BCG infections after BCG instillations was 1% in a registry-based cohort analysis [269]. It has been shown that a maintenance schedule is not associated with an increased risk of side effects compared to an induction course [268]. Side effects requiring treatment stoppage were seen more often in the first year of therapy [270]. Elderly patients do not seem to experience more side effects leading to treatment discontinuation [271] (LE: 2a). No significant difference in toxicity between different BCG strains was demonstrated [266]. Symptoms may be the result of side effects of the BCG treatment or caused by bladder disease (widespread CIS) itself. Consequently, the burden of symptoms is reduced after completion of the treatment in a significant number of patients [272].

Major complications can appear after systemic absorption of the drug. Thus, contraindications of BCG intravesical instillation should be respected (see Section 7.7). The presence of leukocyturia, nonvisible haematuria or asymptomatic bacteriuria is not a contraindication for BCG application, and antibiotic prophylaxis is not necessary in these cases [109, 273, 274] (LE: 3).

Bacillus Calmette-Guérin should be used with caution in immunocompromised patients; e.g., immunosuppression, human immunodeficiency virus (HIV) infection poses relative contraindications [275], although some small studies have shown similar efficacy and no increase in complications compared to non-immunocompromised patients. The role of prophylactic anti-tuberculosis medication in these patients remains unclear [276-278] (LE: 3). The management of side effects after BCG should reflect their type and grade according to the recommendations provided by the International Bladder Cancer Group (IBCG) and by a Spanish group [279, 280] (Table 7.1).

Table 7.1: Management options for side effects associated with intravesical BCG [280-283]

Management options for local side effects (modified from International Bladder Cancer Group)	
Symptoms of cystitis	Phenazopyridine, propantheline bromide, or non-steroidal anti-inflammatory drugs (NSAIDs).
	If symptoms improve within a few days: continue instillations.
	If symptoms persist or worsen: a. Postpone the instillation b. Perform a urine culture c. Start empirical antibiotic treatment
	If symptoms persist even with antibiotic treatment: a. With positive culture: adjust antibiotic treatment according to sensitivity b. With negative culture: quinolones and potentially analgesic anti-inflammatory instillations once daily for 5 days (repeat cycle if necessary) [281].
	If symptoms persist: anti-tuberculosis drugs + corticosteroids.
	If no response to treatment and/or contracted bladder: radical cystectomy.
Haematuria	Perform urine culture to exclude haemorrhagic cystitis if other symptoms present.
	If haematuria persists, perform cystoscopy to evaluate presence of bladder tumour.
Symptomatic granulomatous prostatitis	Symptoms rarely present: perform urine culture.
	Quinolones.
	If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.
	Cessation of intravesical therapy.
Epididymo-orchitis [282]	Perform urine culture and administer quinolones.
	Cessation of intravesical therapy.
	Orchidectomy if abscess or no response to treatment.
Management options for systemic side effects	
General malaise, fever	Generally resolve within 48 hours, with or without antipyretics.
Arthralgia and/or arthritis	Rare complication and considered autoimmune reaction.
	Arthralgia: treatment with NSAIDs.
	Reactive arthritis: NSAIDs.
	If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs [283].

Persistent high-grade fever (> 38.5°C for > 48 h)	Permanent discontinuation of BCG instillations.
	Immediate evaluation: urine culture, blood tests, chest X-ray.
	Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted.
	Consultation with an infectious diseases specialist.
BCG sepsis	Prevention: initiate BCG at least 2 weeks post-transurethral resection of the bladder (if no signs and symptoms of haematuria).
	Cessation of BCG.
	For severe infection: • High-dose quinolones or isoniazid, rifampicin and ethambutol daily for 6 months. • Early, high-dose corticosteroids as long as symptoms persist. • Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or *Enterococcus.*
Allergic reactions	Antihistamines and anti-inflammatory agents.
	Consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.
	Delay therapy until reactions resolve.

7.2.2.4 Optimal BCG schedule

Induction BCG instillations are given according to the empirical 6-weekly schedule introduced by Morales *et al.* [284]. For optimal efficacy, BCG must be given in a maintenance schedule [236-238, 256] (LE: 1a). Many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 to 27 weeks over 3 years [285].

7.2.2.4.1 Optimal number of induction instillations and frequency of instillations during maintenance

The optimal number of induction instillations and frequency of maintenance instillations were evaluated by NIMBUS, a prospective phase III RCT. Safety analysis after 345 randomised patients demonstrated that a reduced number of instillations (3 instillations in induction and 2 instillations at 3, 6 and 12 months) proved inferior to the standard schedule (6 instillation in induction and 3 instillations at 3, 6 and 12 months) regarding the time to first recurrence [286] (LE: 1b). In a RCT including 397 patients CUETO showed that in high-risk tumours a maintenance schedule with only one instillation every 3 months for 3 years was not superior to induction therapy only, which suggested that one instillation may be suboptimal to 3 instillations in each maintenance cycle [287] (LE: 1b).

7.2.2.4.2 Optimal length of maintenance

In their meta-analysis, Böhle *et al.* concluded that at least one year of maintenance BCG is required to obtain superiority of BCG over MMC for prevention of recurrence or progression [236] (LE: 1a).

In a RCT of 1,355 patients, the EORTC has shown that when BCG is given at full dose, 3 years' maintenance (3-weekly instillations 3, 6, 12, 18, 24, 30 and 36 months) reduces the recurrence rate compared to one year in high- but not in intermediate-risk patients. There were no differences in progression or OS. In the 3-year arm, however, 36.1% of patients did not complete the 3-year schedule [288] (LE: 1b). The main reason why these patients stopped treatment was treatment inefficacy, not toxicity.

7.2.2.5 Optimal dose of BCG

To reduce BCG toxicity, instillation of a reduced dose was proposed. However, it has been suggested that a full dose of BCG is more effective in multifocal tumours [289, 290] (LE: 1b). The CUETO study compared one-third dose to full-dose BCG and found no overall difference in efficacy. One-third of the standard dose of BCG might be the minimum effective dose for intermediate-risk tumours. A further reduction to one-sixth dose resulted in a decrease in efficacy with no decrease in toxicity [291] (LE: 1b). The EORTC did not find any difference in toxicity between one-third and full-dose BCG, but one-third dose BCG was associated with a higher recurrence rate, especially when it was given only for one year [270, 288] (LE: 1b). The routine use of one-third dose BCG is complicated by potential technical difficulties in preparing the reduced dose reliably.

7.2.2.6 BCG shortage

A statement by the Panel on BCG shortage can be accessed online:
https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=appendices-publications.

7.2.2.7 *Summary of evidence - BCG treatment*

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical BCG after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

7.2.3 ***Combination therapy***

7.2.3.1 *Intravesical BCG plus chemotherapy versus BCG alone*

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing recurrences but more toxic compared to BCG monotherapy (LE: 1b). Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by one MMC instillation [292]. In a RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [252, 293] (LE: 2). Two meta-analyses demonstrated improved disease-free survival (DFS), but no difference in PFS in patients treated with combination treatment comparing to BCG alone [293, 294].

7.2.3.2 *Combination treatment using interferon*

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [295]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [296]. Additionally, a RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [297] (LE: 1b).

7.2.4 ***Specific aspects of treatment of carcinoma in situ***

7.2.4.1 *Treatment strategy*

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [194, 196]. In this case further treatment according to the criteria summarised in Sections 7.2.1, 7.2.2, 7.5 and 7.6 is mandatory. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [205] (LE: 3).

7.2.4.2 *Cohort studies on intravesical BCG or chemotherapy*

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG [205-208, 298] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [208, 230, 285, 298] (LE: 3).

7.2.4.3 *Prospective randomised trials on intravesical BCG or chemotherapy*

Unfortunately, there have been few RCTs in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [299] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or immunotherapy [237] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [300]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b).

7.2.4.4 *Treatment of CIS in the prostatic urethra and upper urinary tract*

Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona *et al.* found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [301]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [301] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [302]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours) and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection

of the prostate can improve contact of BCG with the prostatic urethra [128, 303] (LE: 3). However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement there are promising results of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [303, 304] (LE: 3).

7.2.4.5 Summary of evidence - treatment of carcinoma in situ

Summary of evidence	**LE**
Carcinoma *in situ* cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, intravesical BCG maintenance instillations increase the complete response rate, the overall percentage of patients who remain disease free, and reduce the risk of tumour progression.	1b

7.3 Intravesical chemoablation and neoadjuvant treatment

Older marker lesion studies have shown that chemoablation with a single intravesical chemotherapy instillation can achieve a complete response in a proportion of patients [305]. In addition, hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with post-operative SI with MMC and TURB only, showed improved long-term RFS among patients treated prior to TURB [306], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, additional neoadjuvant clinical trials were recently published. In recurrent low-risk [307] and recurrent Ta tumours [308], 4 and 6 intravesical MMC instillations achieved complete response in 37% and 57% of the patients, respectively. The former study prematurely stopped recruitment as the anticipated 45% complete response after chemoablation was not achieved. Compared to TURB, less dysuria and incontinence occurred in the intervention arm of the trial. Before routine clinical application, additional high-level evidence with RFS as an outcome measure is required.

7.4 Radical cystectomy for non-muscle-invasive bladder cancer

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27–51% of patients being upstaged to muscle-invasive tumour at RC [162, 309-313] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage have a worse prognosis than those who present with ‘primary’ muscle-invasive disease [314, 315].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life (QoL) and discussed with patients, in a shared decision-making process. It is reasonable to propose immediate RC in those patients with NMIBC who are at very high risk of disease progression (see Section 6.3 and Tables 6.1 and 6.2) [66, 159, 194, 196, 316] (LE: 3).

Early RC is strongly recommended in patients with BCG-unresponsive tumours and should be considered in BCG relapsing HG tumours as mentioned in Section 7.7 and Table 7.3. A delay in RC may lead to decreased disease-specific survival [317] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [318-320] (LE: 3).

7.5 Individual treatment strategy in primary or recurrent tumours after TURB without previous BCG intravesical immunotherapy

The type of further therapy after TURB should be based on the risk groups shown in Section 6.3 and Table 6.1. The stratification and treatment recommendations are based on the risk of disease progression. In particular in intermediate-risk tumours, the 2006 EORTC scoring model may be used (Section 6.1.1.1) to determine a patient’s individual risk of disease recurrence as the basis to decide further treatment on.

Any decisions should reflect the following principles:

- Patients in the low-risk group have a negligible risk of disease progression. The single post-operative instillation of chemotherapy reduces the risk of recurrence and is considered as sufficient treatment in these patients.

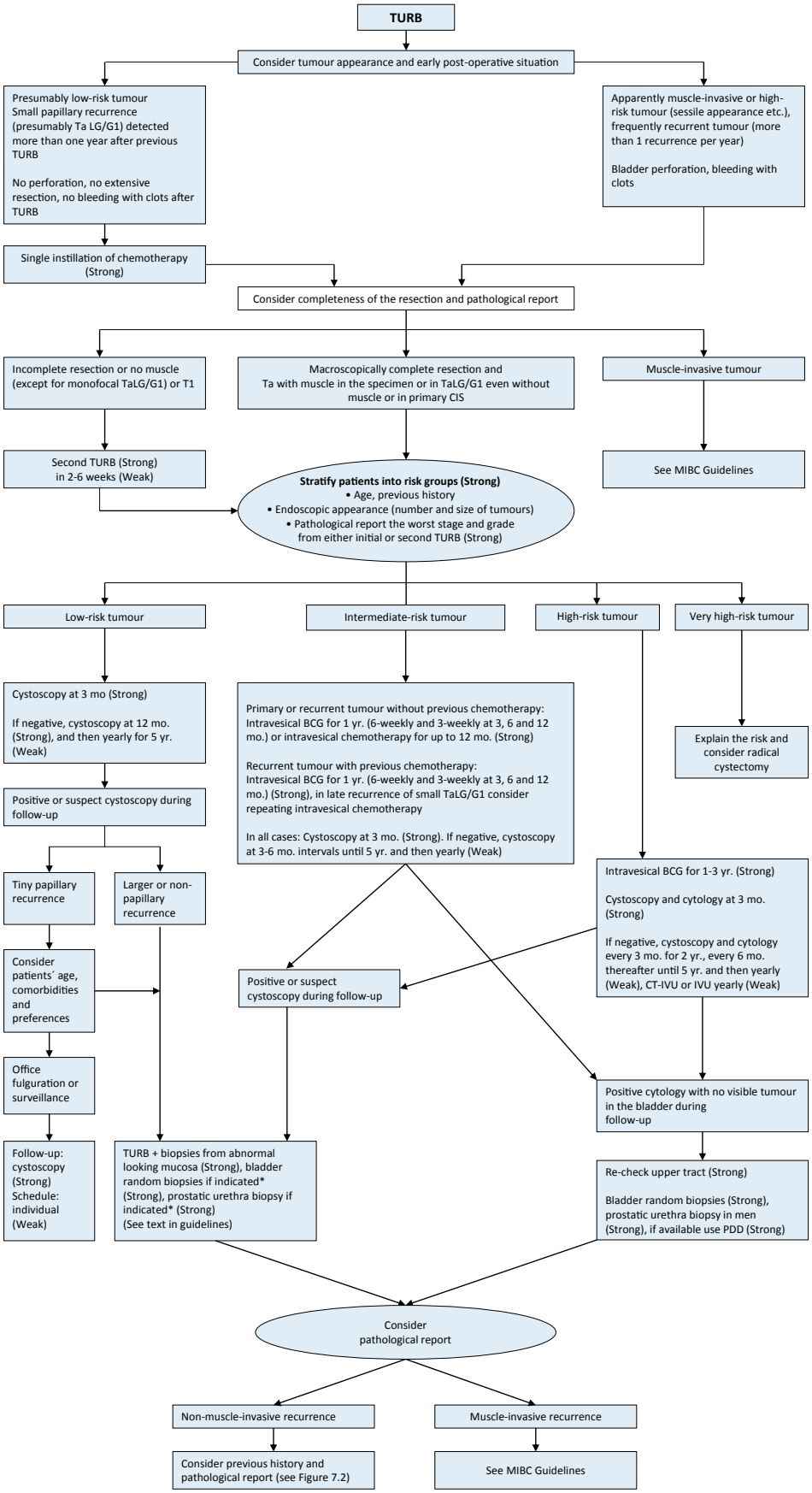
- Patients in the intermediate-risk group have a low risk of disease progression (7.4 and 8.5% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients one-year full-dose BCG treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year, is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.

- Patients in the high-risk group have a high risk of disease progression (14.1 and 14.2% after 10 years according to the 2021 EAU NMIBC scoring model). In these patients full-dose intravesical BCG for one to 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems associated with BCG shortage. Because of the high risk of progression, immediate RC may also be discussed with the patient. Radical cystectomy is the safest approach from oncological point of view, it is, however, associated with the risk of complications and QoL impairment and represents overtreatment in some patients.

- Patients in the very high-risk group have an extremely high risk of tumour progression (53.1 and 58.6% after 10 years according to the 2021 EAU NMIBC scoring model). Immediate RC should be discussed with these patients. In case RC is not feasible or refused by the patient, full-dose intravesical BCG for one to 3 years should be offered.

Figure 7.1 presents a treatment flow chart based on risk category, which may guide management of an individual patient.

Figure 7.1: Treatment strategy in primary or recurrent tumour(s) without previous BCG*


TURB
Consider tumour appearance and early post-operative situation
Presumably low-risk tumour
Small papillary recurrence (presumably Ta LG/G1) detected more than one year after previous TURB
No perforation, no extensive resection, no bleeding with clots after TURB
Apparently muscle-invasive or high-risk tumour (sessile appearance etc.), frequently recurrent tumour (more than 1 recurrence per year)
Bladder perforation, bleeding with clots
Single instillation of chemotherapy (Strong)
Consider completeness of the resection and pathological report
Incomplete resection or no muscle (except for monofocal TaLG/G1) or T1
Macroscopically complete resection and Ta with muscle in the specimen or in TaLG/G1 even without muscle or in primary CIS
Muscle-invasive tumour
Second TURB (Strong) in 2-6 weeks (Weak)
See MIBC Guidelines
Stratify patients into risk groups (Strong)
• Age, previous history
• Endoscopic appearance (number and size of tumours)
• Pathological report the worst stage and grade from either initial or second TURB (Strong)
Low-risk tumour
Intermediate-risk tumour
High-risk tumour
Very high-risk tumour
Cystoscopy at 3 mo (Strong)
If negative, cystoscopy at 12 mo. (Strong), and then yearly for 5 yr. (Weak)
Primary or recurrent tumour without previous chemotherapy: Intravesical BCG for 1 yr. (6-weekly and 3-weekly at 3, 6 and 12 mo.) or intravesical chemotherapy for up to 12 mo. (Strong)
Recurrent tumour with previous chemotherapy: Intravesical BCG for 1 yr. (6-weekly and 3-weekly at 3, 6 and 12 mo.) (Strong), in late recurrence of small TaLG/G1 consider repeating intravesical chemotherapy
In all cases: Cystoscopy at 3 mo. (Strong). If negative, cystoscopy at 3-6 mo. intervals until 5 yr. and then yearly (Weak)
Explain the risk and consider radical cystectomy
Positive or suspect cystoscopy during follow-up
Tiny papillary recurrence
Larger or non-papillary recurrence
Intravesical BCG for 1-3 yr. (Strong)
Cystoscopy and cytology at 3 mo. (Strong)
If negative, cystoscopy and cytology every 3 mo. for 2 yr., every 6 mo. thereafter until 5 yr. and then yearly (Weak), CT-IVU or IVU yearly (Weak)
Consider patients´ age, comorbidities and preferences
Positive or suspect cystoscopy during follow-up
Office fulguration or surveillance
Positive cytology with no visible tumour in the bladder during follow-up
Follow-up: cystoscopy (Strong) Schedule: individual (Weak)
TURB + biopsies from abnormal looking mucosa (Strong), bladder random biopsies if indicated* (Strong), prostatic urethra biopsy if indicated* (Strong) (See text in guidelines)
Re-check upper tract (Strong)
Bladder random biopsies (Strong), prostatic urethra biopsy in men (Strong), if available use PDD (Strong)
Consider pathological report
Non-muscle-invasive recurrence
Muscle-invasive recurrence
Consider previous history and pathological report (see Figure 7.2)
See MIBC Guidelines

** For details and explanations see the text of the guidelines.*
BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; IVU = intravenous urography; MIBC = muscle-invasive bladder cancer; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.6 Treatment of failure of intravesical therapy

7.6.1 Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillations [238] (LE: 1a).

7.6.2 Treatment failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any HG disease occurring during or after BCG therapy, have been proposed (see Table 7.2). Non-muscle-invasive BC may not respond at all (BCG refractory) or may relapse after initial response (BCG relapsing). Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [321].

To be able to specify the subgroup of patients where additional BCG is unlikely to provide benefit, the category of BCG-unresponsive tumour was defined. Further BCG instillations in these patients are associated with an increased risk of progression [209, 322]. The category of BCG-unresponsive tumours comprises BCG-refractory and some of BCG-relapsing tumours (see Table 7.2) [323]. The definition was developed in consultation with the U.S. Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [324].

Non-HG recurrence after BCG is not considered as BCG failure.

Table 7.2: Categories of high-grade recurrence during or after BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months [209, 322, 325] (LE: 3). 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [302] (LE: 4). 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [45, 298, 302] (LE: 1b). 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of HG/G3 (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response [326] (LE: 3).
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [323] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [280].

** Patients with LG recurrence during or after BCG treatment are not considered to be a BCG failure.*

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

7.6.3 Treatment of BCG-unresponsive tumours, late BCG-relapsing tumours, LG recurrences after BCG treatment and patients with BCG intolerance

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Currently, several bladder preservation strategies are being investigated such as cytotoxic intravesical therapies [327-330], device assisted instillations [331-333] intravesical immunotherapy [334, 335], systemic immunotherapy [336] or gene therapy [337-339].

A phase III RCT including predominantly high-risk NMIBC patients failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia provided 35% overall DFS at 2 years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at the discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave-induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [333].

Promising data on BCG-unresponsive cohorts of patients with CIS alone or concomitant to papillary tumours were recently reported following new immunotherapies. Systemic pembrolizumab achieved a 40% complete response rate in a prospective phase II study which was maintained in 48% of patients for up to 12 months (n = 101), resulting in FDA approval of the study drug for this patient population [340]. Promising data from a phase III multicentre RCT with intravesical nadofaragene firadenovec were published recently showing a complete response in 53.4% in patients with BCG-unresponsive CIS [341].

A systematic review and meta-analysis including 4 RCTs and 24 single-arm studies (all currently available prospective studies) assessed bladder-sparing treatments following BCG failure [342]. The significant heterogeneity of both trial designs and patient characteristics included in these studies, the different definitions of BCG failures used, and missing information on prior BCG courses may account for the variability in efficacy for the different compounds assessed across different trials. A higher number of previous BCG courses, BCG refractory/unresponsive or CIS predicted lower response rates. The pooled 12-month response rates were 24% for trials with ≥ 2 prior BCG courses and 36% for those with ≥ 1 BCG courses. Initial response rate did not predict durable responses highlighting the need for longer-term follow-up. More recently, a systematic review assessing 42 prospective trials on bladder preserving treatments after BCG showed that patients with papillary-only recurrences appeared more effectively treated (median recurrence free rates of 44% at 1 year, median progression-free rate 89% at a median follow-up of 19 months) than CIS-containing tumours (median complete response rate 17% at 1 year with a median progression-free rate of 95% at a median follow-up of 12 months), highlighting potential biological differences between these two tumour entities which should be analysed separately when reporting results of clinical trials [343].

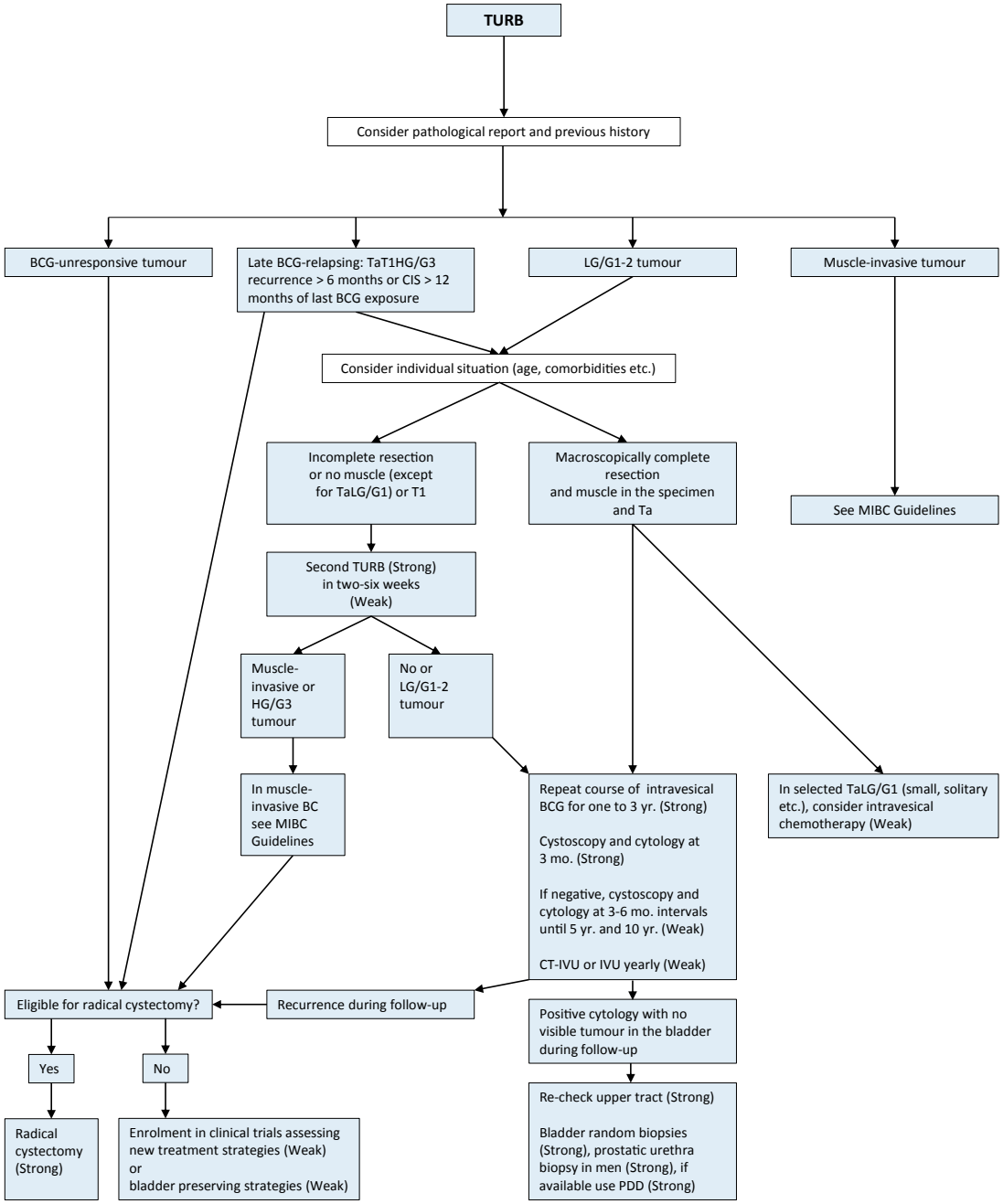
At the present time, treatments other than RC are considered oncologically inferior in patients with BCG-unresponsive disease [209, 322, 325] (LE: 3). Various studies suggest that repeat-BCG therapy is appropriate for non-HG and even for some HG recurrent tumours; namely those relapsing beyond one year after BCG exposure (cases which do not meet the criteria of BCG-unresponsive disease) [344, 345] (LE: 3).

Treatment decisions in LG recurrences after BCG (which are not considered as any category of BCG failure) should be individualised according to tumour characteristics. Little is known about the optimal treatment in patients with high-risk tumours who could not complete BCG instillations because of intolerance.

*7.6.4 **Summary of evidence - treatment failure of intravesical therapy***

Summary of evidence	**LE**
Prior intravesical chemotherapy has no impact on the effect of BCG instillation.	1a
Treatments other than RC must be considered oncologically inferior in patients with BCG-unresponsive tumours.	3

Figure 7.2: Treatment strategy in recurrence during or after intravesical BCG*


TURB
Consider pathological report and previous history
BCG-unresponsive tumour
Late BCG-relapsing: TaT1HG/G3 recurrence > 6 months or CIS > 12 months of last BCG exposure
LG/G1-2 tumour
Muscle-invasive tumour
Consider individual situation (age, comorbidities etc.)
Incomplete resection or no muscle (except for TaLG/G1) or T1
Macroscopically complete resection and muscle in the specimen and Ta
See MIBC Guidelines
Second TURB (Strong) in two-six weeks (Weak)
Muscle-invasive or HG/G3 tumour
No or LG/G1-2 tumour
In muscle-invasive BC see MIBC Guidelines
Repeat course of intravesical BCG for one to 3 yr. (Strong)
Cystoscopy and cytology at 3 mo. (Strong)
If negative, cystoscopy and cytology at 3-6 mo. intervals until 5 yr. and 10 yr. (Weak)
CT-IVU or IVU yearly (Weak)
In selected TaLG/G1 (small, solitary etc.), consider intravesical chemotherapy (Weak)
Eligible for radical cystectomy?
Recurrence during follow-up
Positive cytology with no visible tumour in the bladder during follow-up
Yes
No
Radical cystectomy (Strong)
Enrolment in clinical trials assessing new treatment strategies (Weak) or bladder preserving strategies (Weak)
Re-check upper tract (Strong)
Bladder random biopsies (Strong), prostatic urethra biopsy in men (Strong), if available use PDD (Strong)

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high-grade; IVU = intravenous urography; LG = low-grade; PDD = photodynamic diagnosis; TURB = transurethral resection of the bladder.

7.7 Guidelines for adjuvant therapy in TaT1 tumours and for therapy of carcinoma *in situ*

General recommendations	Strength rating
Counsel smokers with confirmed non-muscle-invasive bladder cancer (NMIBC) to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder (TURB) should be based on the risk groups shown in Section 6.3 and Table 6.1. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net.	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, offer one immediate chemotherapy instillation.	Strong

In patients with intermediate-risk tumours (with or without immediate instillation), one-year full- dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	Strong
In patients with high-risk tumours, full-dose intravesical BCG for one to 3 years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems connected with BCG shortages. Immediate radical cystectomy (RC) may also be discussed with the patient.	Strong
In patients with very high-risk tumours discuss immediate RC. Offer intravesical full-dose BCG instillations for one to 3 years to those who refuse or are unfit for RC.	Strong
Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.	Weak
The definition of 'BCG-unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.	Strong
Offer a RC to patients with BCG-unresponsive tumours.	Strong
Offer patients with BCG-unresponsive tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).	Weak
Recommendations - technical aspects for treatment	
Intravesical chemotherapy	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak
BCG intravesical immunotherapy	
Absolute contraindications of BCG intravesical instillation are: • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection.	Strong

7.8 Guidelines for the treatment of TaT1 tumours and carcinoma *in situ* according to risk stratification

Recommendations	**Strength rating**
EAU risk group: Low	
Offer one immediate instillation of intravesical chemotherapy after transurethral resection of the bladder (TURB).	Strong
EAU Risk Group: Intermediate	
In all patients either one-year full-dose Bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB.	Strong
EAU risk group: High	
Offer intravesical full-dose BCG instillations for one to 3 years or discuss immediate radical cystectomy (RC).	Strong

EAU risk group: Very High	
Offer RC or intravesical full-dose BCG instillations for one to 3 years to those who refuse or are unfit for RC.	Strong

Table 7.3: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC).
	2. Enrolment in clinical trials assessing new treatment strategies.
	3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG relapsing: TaT1 HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation.
	2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy.
	2. Radical cystectomy.

8. FOLLOW-UP OF PATIENTS WITH NMIBC

As a result of the risk of recurrence and progression, patients with NMIBC need surveillance following therapy. However, the frequency and duration of cystoscopy and imaging follow-up should reflect the individual patient's degree of risk. Using the EAU NMIBC prognostic factor risk groups (see Section 6.3, Tables 6.1 and 6.2) or further prognostic models for specific patient populations (see Chapter 6), the short- and long-term risks of recurrence and progression in individual patients may be predicted and the follow-up schedule adapted accordingly (see Section 8.1) [194, 196]. However, recommendations for follow-up are mainly based on retrospective data and there is a lack of RCTs investigating the possibility of safely reducing the frequency of follow-up cystoscopy.

When planning the follow-up schedule and methods, the following aspects should be considered:

- The prompt detection of muscle-invasive and HG/G3 non-muscle-invasive recurrence is crucial and the percentage of tumours missed should be as low as possible because a delay in diagnosis and therapy can be life-threatening. Therefore, the best surveillance strategy for these patients will continue to include frequent cystoscopy and cytology.
- Tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy [346, 347] (LE: 2b). Fulguration of small papillary recurrences on an outpatient basis could be safe [348] (LE: 3). Multiple authors have suggested active surveillance in selected cases [349-351] (LE: 3/2a).
- The first cystoscopy after TURB at 3 months is an important prognostic indicator for recurrence and progression [202, 208, 352-354] (LE: 1a). Therefore, the first cystoscopy should always be performed 3 months after TURB in all patients with TaT1 tumours and CIS.
- In tumours at low risk, the risk of recurrence after 5 recurrence-free years is low [353] (LE: 3). Therefore, in low-risk tumours, after 5 years of follow-up, discontinuation of cystoscopy or its replacement with less-invasive methods can be considered [354].
- In tumours originally intermediate-, high risk, or very high risk treated conservatively, recurrences after ten years tumour-free are not unusual [355] (LE: 3). Therefore, life-long follow-up is recommended [354].
- The follow-up strategy must reflect the risk of extravesical recurrence (prostatic urethra in men and UUT in both genders).
- The risk of UUT recurrence increases in patients with multiple- and high-risk tumours [85] (LE: 3).
- There may be a role for newer methods of tumour visualisation in follow-up cystoscopy. In a prospective study of blue light flexible cystoscopy (BLFC) for surveillance of NMIBC, BLFC alone showed an abnormality in 8% of which half had biopsy-confirmed BC [356]. On the other hand, a prospective study of narrow-band imaging (NBI) for NMIBC surveillance failed to show any benefit for NBI over white light cystoscopy alone [357].

- The current status of urine cytology and urinary molecular marker tests is discussed in detail in Sections 5.5, 5.6 and 5.7. Non-muscle-invasive BC follow-up strategies include urine cytology and urinary molecular marker tests as adjunct (or companion) tests to improve detection at the time of flexible cystoscopy or as replacement tests to reduce the number of flexible cystoscopies.
- The role of urinary cytology or urinary molecular markers as an adjunct to cystoscopy (companion test) in the follow-up of NMIBC has been investigated [106, 107, 119, 120, 124]. One prospective RCT found that knowledge of positive test results (microsatellite analysis) can improve the quality of follow-up cystoscopy [125] (LE: 1b), supporting the adjunctive role of a non-invasive urine test performed prior to follow-up cystoscopy [125] (see Section 5.7.3).
- In order for urinary markers to reduce or replace cystoscopy altogether, they should be able to detect recurrence across all risk groups. However, currently the limitation of urinary cytology and current urinary markers is their low sensitivity for LG recurrences [101, 107] (see Section 5.7.3) (LE: 1b).
- In patients initially diagnosed with Ta LG/G1–2 BC, US of the bladder or a urinary marker may be a mode of surveillance in case cystoscopy is not possible or refused by the patient [123, 124, 358].
- According to current knowledge, no urinary marker can replace cystoscopy during follow-up or lower cystoscopy frequency in a routine fashion.

8.1 Summary of evidence and guidelines for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer

Summary of evidence	LE
The first cystoscopy after transurethral resection of the bladder at 3 months is an important prognostic indicator for recurrence and progression.	1a
The risk of upper urinary tract recurrence increases in patients with multiple- and high-risk tumours.	3

Recommendations	Strength rating
Base follow-up of TaT1 tumours and carcinoma *in situ* (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	Weak
Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong
During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with Ta LG/G1–2 bladder cancer, use ultrasound of the bladder, and/or a urinary marker during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is open access available on the European Association of Urology website: https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/?type=panel.

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11. CITATION INFORMATION

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1. INTRODUCTION

Lower urinary tract symptoms (LUTS) encompass storage, voiding and post-micturition symptoms [1]. Storage symptoms include frequency, urgency, nocturia and urinary incontinence (UI) (stress UI [SUI], urgency UI [UUI] and mixed UI [MUI]). Voiding symptoms include hesitancy, intermittency, slow stream, straining, splitting or spraying of the urinary stream and terminal dribble. Post-micturition symptoms include post-void dribbling and feeling of incomplete bladder emptying. Lower urinary tract symptoms are often broadly classified into clinical syndromes/entities such as overactive bladder (OAB), underactive bladder (UAB), UI, nocturia, dysfunctional voiding, or genito-urinary fistulae.

LUTS are common in women [2-5] and cause a great deal of distress and embarrassment [6], as well as significant costs to both individuals and society [7]. Estimates of prevalence vary according to the definition and population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost [7].

1.1 Aim and objectives

These Guidelines from the European Association of Urology (EAU) Working Panel on Non-neurogenic Female LUTS are written by a multidisciplinary group, primarily for urologists, but are likely to be referred to by other professional groups. The guidelines aim to provide sensible and practical evidence-based guidance on the clinical problems associated with female LUTS rather than an exhaustive narrative review. Such reviews for UI and other LUT syndromes are already available from the International Consultation on Incontinence [8] and other sources. Therefore, these EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of LUTS/UI in detail. The focus of these guidelines is on assessment and treatment, reflecting clinical practice, and they do not consider women with LUTS caused by neurological disease, or LUTS occurring in children, as these are covered by complementary EAU Guidelines [9, 10].

The current guidelines provide:

- A clear description of the assessment and treatment of common clinical problems. This can provide the basis for both individual patient management and for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance in those areas of practice for which there is little or no high-quality evidence.

The latest edition of the guideline has seen a significant expansion of scope from UI to non-neurogenic female LUTS. The primary consideration here is to include the significant population of women with functional urological conditions not necessarily associated with UI that were hitherto not accounted for in previous guidelines. Secondary considerations are to align more cohesively with the existing Non-neurogenic Male LUTS Guidelines. As a consequence of the anatomical and physiological differences between the male and female LUT, the prevalence, pathophysiology, diagnostic approach and management of male and female LUTS differ widely. For that reason, the EAU Guidelines Office decided to provide gender-specific guidelines on LUTS and UI.

1.2 Panel composition

The EAU Non-neurogenic Female LUTS Panel consists of a multidisciplinary group of experts, including urologists, a uro-gynaecologist, a urodynamic scientist, physiotherapists, a nurse practitioner continence care and patient advocates. All experts involved in the production of this document have submitted potential conflict of interest statements that can be viewed on the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions that require consideration together with the full-text versions. All documents are accessible through the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

1.4 Publication history

The first EAU Urinary Incontinence Guidelines were published in 2001. The guidelines have been modified since to broaden its scope specifically to include other female LUTS as of 2021. Except for pelvic organ prolapse, all other sections of the 2022 Female LUTS Guidelines have been fully updated.

2. METHODS

2.1 Introduction

For the 2021 Non-neurogenic Female Lower Urinary Tract Symptoms Guidelines, the existing text of the 2018 Urinary Incontinence Guidelines was restructured and expanded. The Patient/Population, Intervention, Comparison and Outcome (PICO) question-based format of the text was modified to improve readability, although the underlying PICO structure still informs search strategies.

For the 2022 Non-neurogenic Female Lower Urinary Tract Symproms Guidelines, databases searched included Medline, Embase, and the Cochrane Libraries, covering a time frame between 12 June 2020 and 07 September 2021 with a focus on high-level evidence only (systematic reviews and meta-analyses). A total of 187 unique records were identified, retrieved and screened for relevance. Detailed search strategies are available online: https://uroweb.org/guideline/non-neurogenic-female-luts/?type=appendices-publications.

For the 2022 edition of the guidelines a *de novo* systematic review (SR) was undertaken by the Panel on the subject of overactive bladder syndrome [11]. Full publication of the SR results are pending; however, the preliminary results have informed the corresponding sections of this guidelines update.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [12, 13]. Each strength rating form addresses a number of key elements, namely:

1. overall quality of the evidence which exists for the recommendation; references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [14];
2. magnitude of the effect (individual or combined effects);
3. certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. balance between desirable and undesirable outcomes;
5. impact of patient values and preferences on the intervention;
6. certainty of those patient values and preferences.

These key elements are the basis that panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words strong or weak [15]. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The guidelines were extensively peer reviewed prior to publication in 2021.

2.3 Future goals

- Systematic review of pelvic organ prolapse;
- Systematic review of synthetic/mesh-related mid-urethral sling complications;
- Systematic review of the diagnosis and treatment of UAB in women.

3. DIAGNOSIS

3.1 History and physical examination

Taking a thorough clinical history is fundamental to the process of clinical evaluation. Despite the lack of high-level evidence to support taking a history, there is universal agreement that it should be the first step in the assessment of anyone with LUTS. The history should include a full evaluation of LUTS, as well as sexual, gastrointestinal and neurological symptoms. Details of urgency episodes, the type, timing and severity of UI, and some attempt to quantify symptoms should also be made. The history should help to categorise LUTS as storage, voiding and post-micturition symptoms, and classify UI as SUI, UUI, MUI or overflow incontinence; the

latter being defined as “the complaint of UI in the symptomatic presence of an excessively (over-) full bladder (no cause identified)” [16].

The history should also identify patients who need referral to an appropriate clinic/specialist. These may include patients with associated pain, haematuria, history of recurrent urinary tract infection (UTI), pelvic surgery or radiotherapy, constant leakage suggesting a fistula (see Section 4.8), new-onset enuresis or suspected neurological disease. A neurological, obstetric and gynaecological history may help to understand the underlying cause and identify factors that may affect treatment decisions. Guidance on history-taking and diagnosis in relation to UTIs, neuro-urological conditions and chronic pelvic pain (CPP) can be found in the relevant EAU Guidelines [9, 17, 18]. Patients should also be asked about other comorbidity as well as smoking status, previous surgical procedures and current medications, as these may affect LUTS.

There is little evidence from clinical trials that carrying out a clinical examination improves outcomes, but widespread consensus suggests that clinical examination remains an essential part of assessment of patients with LUTS. Examination should include abdominal examination, to detect an enlarged urinary bladder or other abdominal mass, and digital examination of the vagina and/or rectum. Pelvic examination in women includes assessment of oestrogen status, pelvic floor muscle (PFM) function and careful assessment of any associated pelvic organ prolapse (POP). A cough stress test is necessary to look for SUI. Among women with genital prolapse, the cough test was found to show good agreement with urodynamic studies (UDS) in the detection of SUI [19]. Urethral mobility can be assessed. Pelvic floor muscle contraction strength can also be assessed digitally. A focused neuro-urological examination should also be routinely undertaken.

3.1.1 Summary of evidence and recommendation for history taking and physical examination

Summary of evidence	LE
History taking including symptoms and comorbidity and focused physical examination are essential parts of the evaluation of women with LUTS.	4

Recommendation	Strength rating
Take a complete medical history including symptoms and comorbidity and perform a focused physical examination for evaluation of women with LUTS.	Strong

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires/scales/indices, patient-reported outcome measures (PROMs) and health-related quality of life (QoL) measures. The latter include generic or condition-specific measures. Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, should have been shown to be sensitive to change. The US Food and Drug Administration (FDA) published guidance for industry on PROM instruments (questionnaires) in 2009 [20].

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies included mixed populations (men and women). This limits the extent to which results and conclusions from these studies can be applied to particular LUT syndromes in women. Some questionnaires (ICIQ-FLUTS, QUID, 3IQ, ICIQ-SF) have potential to discriminate UI types in women [21-23]. Others have been developed to measure symptoms and bother in OAB (OABQ-SF, B-SAQ) and other specific conditions. A newly developed patient assessment tool, the OAB- Bladder Assessment Tool (OAB-BAT), was found to be a valid and reliable OAB PROM that includes symptoms, bother, impacts and satisfaction with treatment [24]. A systematic review (SR) included 22 studies that assessed eleven case-finding tools for OAB. All tools were found to have good sensitivity and specificity for OAB or incontinence symptoms. The B-SAQ was the only tool in this SR to include screening for “red- flag” symptoms such as haematuria and pain, and it has also been validated in a primary care setting [25]. Some questionnaires are responsive to change and may be used to measure outcomes, although evidence for this is inconsistent [26, 27].

A SR including 73 studies assessed 27 specific and six generic instruments that measure QoL in women with UI. In this review, IQoL was found to be the most psychometrically robust disease-specific tool for use in English-speaking women with UI. It had the highest level of evidence for sufficient internal consistency, test-retest reliability, measurement error and hypothesis testing for construct validity. It is also the most translated instrument. Evidence on the performance of generic QoL tools for this population is limited [28]. There is no evidence to indicate whether use of QoL or condition-specific questionnaires has an impact on outcome of treatment.

Detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of these guidelines. For more information, we recommend the 6th International Consultation on Incontinence review on PRO assessment [29]. To date, there is not one questionnaire that fulfils all requirements for assessment of women with LUTS. Clinicians must evaluate the tools that exist, for use alone or in combination, for assessment and monitoring of treatment outcome [30]. The questionnaires can be found on the following websites: www.iciq.net, https://eprovide.mapi-trust.org, www.pfizerpcoa.com, www.ncbi.nlm.nih.gov.

3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	LE
Validated condition-specific symptom scores assist in the screening for and categorisation of LUTS.	3
Validated symptom scores measure the severity of UI and LUTS.	3
Both condition-specific and general health status questionnaires measure current health status and change following treatment.	3
Patient questionnaires cannot replace a detailed patient consultation and should only be used as part of a complete medical history.	4

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised initial assessment and follow-up of female LUTS.	Strong

3.3 Bladder diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of LUT dysfunction. Bladder diaries are a semi-objective method of quantifying symptoms, such as frequency of UI events, number of nocturia episodes, etc. They also quantify urodynamic variables, such as voided volume, 24-hour urine volume or nocturnal total urine volume.

Discrepancy between diary recordings and the patient rating of symptoms, e.g., frequency of UI, can be useful for patient counselling. Fluid intake and voided volume measurement can be used to support diagnoses and management planning, for example in OAB, and for identifying 24-hour or nocturnal polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a bladder diary is unlikely to accurately report 24-hour urine output.

Consensus terminology is now well-defined and widely accepted [1, 31]. However, the terms micturition diary, frequency/volume chart, bladder diary and voiding diary, have been used interchangeably for many years, but only bladder diaries include information on fluid intake, times of voiding, voided volumes, UI episodes, pad usage, degree of urgency and severity of UI recorded for at least 24 hours. When reviewing the evidence, all synonymous search terms have been included.

Two studies have demonstrated the reproducibility of diaries in both men and women [32, 33]. Another two studies have shown the feasibility, reliability and validity of the bladder diary [34, 35]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded by uroflowmetry [36, 37]. Another study found that keeping a bladder diary had a therapeutic benefit [38].

A number of observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [39-42]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance [43, 44]. Diary durations between three and seven days are routinely reported in the literature.

3.3.1 Summary of evidence and recommendations for bladder diaries

Summary of evidence	LE
Bladder diaries of 3–7-days duration are reliable tools for objective measurement of mean voided volume, day- and night-time frequency, and UI episode frequency.	2b
Bladder diaries are sensitive to change and are a reliable outcome measure.	2b

Recommendations	Strength rating
Ask patients with LUTS to complete a bladder diary as part of the standardised assessment of female LUTS.	Strong
Use a bladder diary with a duration of ≥ 3 days.	Strong

3.4 Urinalysis and urinary tract infection

Reagent strip (dipstick) urinalysis may indicate proteinuria, haematuria or glycosuria, or suggest UTI requiring further assessment. Please refer to the Urological Infections Guidelines for diagnosis and treatment of UTI [17].

Urine dipstick testing is a useful adjunct to clinical evaluation in patients in whom urinary symptoms are suspected to be due to UTI. Urinalysis negative for nitrite and leukocyte esterase may exclude bacteriuria in women with LUTS [45], and should be included, with urine culture when necessary, in the evaluation of all patients with LUTS. Urinary incontinence or worsening of LUTS may occur during UTI [46] and existing UI may worsen [47]. The rate and severity of UI were unchanged after eradication of asymptomatic bacteriuria in nursing home residents [48].

3.4.1 Summary of evidence and recommendations for urinalysis

Summary of evidence	LE
Urinalysis negative for nitrite and leukocyte esterase may exclude bacteriuria in women with LUTS.	3
UI may be a symptom during UTI, and LUTS may increase during UTI.	3
The presence of UTI worsens existing symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	Strength rating
Perform urinalysis as a part of the initial assessment of patients with LUTS.	Strong
If UTI is present with LUTS, reassess the patient after treatment.	Strong
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve UI.	Strong

3.5 Post-void residual volume

Post-void residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It is a measure of voiding efficiency, and results from a number of contributing factors. The detection of significant PVR volume is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract (UUT) dilatation and renal insufficiency. Both BOO and/or detrusor underactivity (DU) can potentially contribute to the development of significant PVR volume. Post-void residual volume can be measured by catheterisation or ultrasound (US).

Most studies investigating PVR volume have assessed mixed populations including those with neurogenic UI. In general, the data on PVR volume can be applied with caution to women with non-neurogenic LUTS. The results of studies investigating the best method of measuring PVR volume [48-53] have led to the consensus that US measurement of PVR volume is preferable to catheterisation due to its favourable risk–benefit profile.

The prevalence of significant PVR volume among patients with LUTS is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. In peri- and postmenopausal women without significant LUTS or pelvic organ symptoms, 95% had a PVR volume < 100 mL [54]. In women with UUI, PVR volume > 100 mL was found in only 10% of cases [55]. Other research has found that a high PVR volume is associated with POP, voiding symptoms and an absence of SUI [54, 56-58]. In women with SUI, the mean PVR volume was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having PVR volume > 100 mL [59]. Some authors have suggested that it is reasonable to consider a PVR volume > 100 mL to be significant, although many women may remain asymptomatic and hence it is imperative to consider the clinical context [55]. There is no consensus on what constitutes a significant PVR volume in women; therefore, the Panel suggests the additional use of bladder volume efficiency (BVE). Bladder volume efficiency is the proportion of the total bladder volume that is voided by the patient. Bladder volume efficiency can be calculated as a percentage: BVE = voided volume (VV)/(VV+PVR) × 100. This may be a more reliable parameter to evaluate poor voiding [46].

3.5.1 *Summary of evidence and recommendations for post-void residual volume*

Summary of evidence	LE
LUTS are associated with a higher PVR volume compared to asymptomatic population groups.	2

Recommendations	Strength rating
Measure post-void residual (PVR) volume in patients with LUTS during initial assessment.	Strong
Use ultrasound to measure PVR volume.	Strong
Monitor PVR volume in patients receiving treatments that may cause or worsen voiding dysfunction.	Strong
Provide bladder volume efficiency as an additional parameter when measuring PVR volume.	Weak

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome or facilitate discussion during counselling. The simplest form of urodynamic evaluation is uroflowmetry. The maximum flow rate (Q_{max}), the volume voided and the shape of the curve in addition to the PVR volume (see above) are the most important aspects to be assessed [29]. The bladder should be sufficiently full because of the volume dependency of Q_{max} [60, 61]. A minimum voided volume of 150 mL is advised in men, but there is little evidence to suggest a volume threshold in women. It is relevant to ask the patient whether or not the voiding is representative.

Invasive urodynamic tests are sometimes performed prior to invasive treatment of LUTS. These tests include multichannel cystometry and pressure–flow studies, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry and Valsalva leak point pressure (VLPP). The International Continence Society (ICS) and the United Kingdom Continence Society (UKCS) provide standards to optimise urodynamic test performance and reporting [62, 63]. A characteristic of a good urodynamic study is that the patient's symptoms are replicated, recordings are checked for quality control, and results interpreted in the context of the clinical problem, remembering that there may be physiological variability within the same individual [62]. Non-invasive alternatives for measurement of detrusor pressure and BOO include transabdominal wall near-infrared spectroscopy and US detrusor wall thickness analysis, but as yet, these techniques have not been adopted into routine clinical practice [29].

Further condition-specific information regarding the role of urodynamic testing in OAB, SUI, BOO and UAB can be found in respective sections of these guidelines.

3.6.1 *Variability*

In common with most physiological tests there is variability in urodynamic results. This has consequences for the reproducibility, diagnostic accuracy and predictive value of urodynamic testing. It has been stated that, at least in the case of cystometry and pressure–flow studies, one set of measurements suffices, but only if the patient's symptoms have been replicated [62]. Contradictory findings have been reported in studies assessing same-session repeatability of cystometric and pressure–flow studies [64, 65]. There is also conflicting evidence about the reproducibility of maximum urethral closure pressure (MUCP) measurement [64, 65]. One method of recording MUCP cannot be compared meaningfully to another [65, 66]. Valsava leak point pressure measurement is not standardised and there is minimal evidence about its reproducibility. No studies on the reproducibility of ambulatory monitoring in non-neurological patients have been published [29].

3.6.2 *Diagnostic accuracy*

Clinical diagnosis and cystometric findings sometimes do not correlate [67, 68] and asymptomatic women may have abnormalities on urodynamic testing. As the urodynamic diagnosis is often taken as the benchmark in the assessment of LUT function, this implies that other tests of LUT function may be biased. The diagnostic accuracy of urethral pressure profilometry [69] and urethral retro-resistance pressure measurement in SUI is poor [29]. Valsava leak point pressure did not reliably assess UI severity in a cohort of women selected for surgical treatment of SUI [70]. Urethral pressure reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [71]. Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry does, but the clinical relevance of this is also uncertain [72, 73].

A pressure–flow study, that is, the simultaneous measurement of flow rate and detrusor pressure during voiding, can reveal whether a poor flow rate and PVR volume are due to BOO, poor bladder contraction

strength/detruser underactivity (DU), or a combination of both. Also, it may provide information on the degree of pelvic floor relaxation and thus diagnose dysfunctional voiding. Several proposals to define BOO in women have been made. These definitions are based on detrusor pressure, either $P_{det}Q_{max}$ or the maximum value $P_{det.max}$, and the Q_{max} value, either during the pressure–flow study or during uroflowmetry. These measures are sometimes combined with the findings during fluoroscopic imaging (see Section 4.5.4.8) [74, 75]. Unlike the situation in men, there is no widely accepted threshold for BOO diagnosis in women. Bladder contraction strength parameters are derived from detrusor pressure and flow rate during a pressure–flow study or from stop tests [75], but again, validation is poor. Although these parameters estimate the strength of the contraction, they ignore its speed and persistence (see Section 4.4.3.2) [76]. A video-urodynamic study can be useful to detect the site of obstructed voiding, which may be anatomical or functional [77]. Also, video-urodynamics may detect bladder diverticulum or gross reflux as a pressure-absorbing reservoir.

3.6.3 ***Predictive value***

Performing urodynamic evaluation is only useful if it leads to more effective clinical care and better outcomes. A Cochrane review of eight randomised controlled trials (RCTs) showed that use of urodynamic tests in women with UI increased the likelihood of prescribing drugs and did not increase the likelihood of undergoing surgery. However, there was no evidence that this influence on decision-making altered the clinical outcome of treatment [78]. Most RCTs addressed the utility of urodynamic tests on SUI only, including women with uncomplicated SUI. A meta-analysis including four RCTs comparing surgical outcomes in women with self-reported SUI (or stress-predominant MUI) who were investigated via urodynamics with women who had office evaluation only, found that there was no difference in cure and complication rates [79]. In contrast, a large retrospective multicentre study found that only 36% of patients were defined as uncomplicated according to the definitions used in large RCTs [80]. The urodynamic observations were not consistent with the pre-urodynamic diagnosis in 1276 out of 2053 patients (62.2%). Voiding dysfunctions were urodynamically diagnosed in 394 patients (19.2%) and planned surgery was cancelled or modified in 304 of 1582 patients (19.2%) in whom data were available, due to the urodynamic findings [81].

The predictive value of urethral function tests remains unclear. In observational studies, there was no consistent correlation between the results of these tests and subsequent success or failure of SUI surgery [40-42, 82]. The same was true in a secondary analysis of an RCT [83].

The presence of preoperative detrusor overactivity (DO) in women with stress-predominant MUI has been associated with postoperative UUI but did not predict overall treatment failure following mid-urethral sling (MUS) surgery or colpo-suspension [83]. The urodynamic diagnosis of DO had no predictive value for treatment response in studies on antimuscarinics, onabotulinumtoxinA and sacral nerve stimulation in patients with OAB symptoms [84, 85]. Augmentation cystoplasty aims to abolish DO, improve bladder compliance and increase functional bladder capacity but there is no evidence to guide whether or not preoperative urodynamics are predictive of outcome. Most clinicians would, however, consider preoperative urodynamics as essential prior to contemplating augmentation cystoplasty.

A pressure–flow study is capable of discriminating BOO from DU as a cause of voiding dysfunction. The predictive value of parameters derived from such a study for voiding dysfunction after a surgical procedure for SUI is however low. A low preoperative flow rate and a low detrusor voiding pressure have been shown to correlate with voiding dysfunction after a tension-free vaginal tape (TVT) and an autologous fascial sling procedure, respectively [86-88]. Bladder contraction strength parameters combining flow rate and detrusor pressure only poorly predicted voiding dysfunction after autologous fascial sling [89]. *Post hoc* analysis of two high-quality surgical trials of TVT, Burch colpo-suspension and autologous fascial sling showed that no preoperative urodynamic parameter predicted postoperative voiding dysfunction in a selected population of women with low preoperative PVR volume [90, 91].

The Panel recognises that it may be valuable to use urodynamic test results to select the optimum management strategy; however, there is inconsistent evidence regarding the predictive value of such tests. When urodynamics and clinical assessment (i.e., by history and examination) are in disagreement, there needs to be a careful re-evaluation of the clinical symptoms and investigation results to ensure that the diagnosis is correct before invasive treatments are contemplated. Expert opinion recognises urodynamic testing as the most comprehensive analysis of LUT function. The primary aim of urodynamics includes reproduction of the patient's symptoms. The information one obtains from urodynamics may be very valuable to discuss and manage expectation regarding invasive treatment.

3.6.4 Summary of evidence and recommendations for urodynamics

Summary of evidence	LE
Urodynamics provide comprehensive analysis of LUT function.	4
Most urodynamic parameters show variability within the same session and over time, and this may limit clinical interpretation.	3
Different techniques of measuring urethral function may have good test–retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.	3
There may be inconsistency between history and urodynamic results.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a
Preoperative urodynamics in women with uncomplicated, clinically demonstrable SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the results of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that preoperative DO is associated with surgical failure of MUS in women.	3
The presence of preoperative DO may be associated with persistence of urgency postoperatively in women undergoing surgery for SUI.	3

Recommendations	Strength rating
Adhere to good urodynamic practice standards as described by the International Continency Society when performing urodynamics in patients with LUTS.	Strong
Do not routinely carry out urodynamics when offering treatment for uncomplicated stress urinary incontinence.	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated overactive bladder symptoms.	Strong
Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of urinary incontinence as they are primarily tests of urethral function.	Strong

3.7 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, as well as provide an objective evidence of response to treatment.

The clinical utility of pad tests in woman with UI has been assessed in two SRs [92, 93]. A 1-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise, with variation according to activity level [94]. A pyridium pad test showed fair agreement with UDS in the detection of SUI among women with genital prolapse, particularly in identifying occult incontinence in up to 10% of prolapse patients [19]. A pyridium pad test involves patients taking pyridium 200 mg three times daily, for a day, recording if an orange stain is noted on the pad and qualifying the type of leakage associated with the staining as either stress or urgency.

A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated with the degree of provocation increased [95]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [92, 96, 97]. Pad tests are responsive to change following successful treatment [98]. Pad testing using a standardised bladder volume (50% of cystometric capacity) was suggested to allow for a more reliable assessment of UI in a small study of 25 women [99]. There is no evidence that one type of pad test is superior to another.

3.7.1 Summary of evidence and recommendations for pad testing

Summary of evidence	LE
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2

Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2
Pad tests can be a useful tool in the research setting and are an optional investigation in clinical practice.	4

Recommendations	Strength rating
When a pad test is performed, use a standardised duration and activity protocol.	Strong
Use a pad test when quantification of urinary incontinence is required, especially to assess response to treatment.	Weak

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause LUTS. In clinical practice, imaging is used to understand the relationship between anatomy and function. Ultrasound and magnetic resonance imaging (MRI) have largely replaced x-ray imaging in the evaluation of the pelvic floor. Ultrasound is sometimes preferred to MRI because of its ability to produce three-dimensional (3D) and 4D (dynamic) images at lower cost and wider availability.

There is no need for UUT imaging unless a high-pressure bladder, severe POP or chronic urinary retention is suspected or diagnosed, or abnormal renal function tests are observed. In cases of suspected UI caused by an UUT anomaly or uretero-vaginal fistula, UUT imaging (urography, computed tomography [CT]) may be indicated [100].

*3.8.1 **Ultrasound***

Ultrasonography of the LUT plays a role in the differential diagnosis of women with LUTS and in cases presenting with haematuria.

Ultrasonography has been used in the evaluation of UI and pelvic floor since the 1980s. Different imaging approaches, such as abdominal, transvaginal, transrectal, perineal and transurethral are described. The bladder neck and urethra are easily visible and measurements can be done at rest and during straining, coughing and pelvic floor contraction. The parameters assessed in the diagnosis of SUI, for example, include bladder neck mobility or descent, urethro-vesical angle and urethral rotation [101, 102]. Ultrasonography can be used to assess PFMs and their function. Contraction of PFM results in displacement of pelvic structures that can easily be imaged on US. Integrity of the levator ani muscle can be determined by 3D transperineal US. Ultrasound may also provide information on the anatomical changes of the LUT and pelvic floor associated with persistence of symptoms post-treatment [103]. The specific role of US is discussed in the condition-specific sections of these guidelines where applicable.

*3.8.2 **Detrusor wall thickness***

As OAB syndrome is linked to DO, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). Transvaginal US seems to be more accurate with less inter-observer variability than transabdominal and transperineal approaches [104]. Several cut-off points have been suggested, from 4.4 to 6.5 mm. Other studies are contradictory and did not find this correlation. No consensus exists as to the relationship between OAB and increased BWT/DWT [105], and there is no evidence that BWT/DWT imaging improves management of OAB. There is no widely accepted, standardised bladder volume for bladder wall thickness measurement.

In a retrospective study including 227 women with symptoms of voiding difficulty (hesitancy, intermittency and poor stream), 74 (32.6%) were diagnosed with voiding dysfunction on the basis of free uroflowmetry and residual urine. While controlling for the effect of DO, the relationships between DWT and different parameters of voiding function in pressure–flow studies and free uroflowmetry were examined. The results indicated that DWT was not associated with any urodynamic parameters that may indicate BOO [106].

*3.8.3 **Magnetic resonance imaging***

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [107]. However, there is a large variation in MRI interpretation between observers [108] and little evidence to support its clinical usefulness in the management of LUTS/UI. There is no conclusive evidence that MRI evaluation of POP is more clinically useful than vaginal examination. Studies have assessed the use of imaging to assess the mechanism of MUS insertion for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not of the bladder neck [109]. Following MUS, a wider gap between pubic symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [110].

3.8.3.1 Summary of evidence and recommendation for imaging

Summary of evidence	LE
There is no consistent evidence that routine urinary tract imaging is useful in the evaluation or management of LUTS.	3
There is no consistent evidence that BWT/DWT measurement is useful in the management of OAB.	3

Recommendation	Strength rating
Do not routinely carry out imaging of the upper urinary tract or lower urinary tract as part of the assessment of LUTS.	Strong

3.9 Urinary biomarkers and microbiome

Interest in the role of urinary biomarkers for the diagnosis of LUT dysfunction has increased in recent years. Nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), prostaglandin E2, adenosin triphosphate (ATP) and purinergic receptors (P2X) in bladder tissue have been studied as biomarkers for OAB. Serum beta natriuretic peptide (BNP), urinary 6-sulfatoxymelatonin and C-reactive protein (CRP), melatonin, vasopressin levels have been studied in relation to nocturia. For SUI, urinary IL 12-70, urinary NGF, N-telopeptide of type I collagen (NTx) and urinary microbiome have been studied. Currently, studies investigating urinary biomarkers are methodologically limited often due to failing to control for confounding variables and results are conflicting [111].

Another area of discovery is the role of urinary microbiome in identifying and differentiating various types of UI and other LUT disease in women. A SR described studies showing differences in the types and relative proportions of bacteria such as *Lactobacillus, Gardnerella, and Atopobium vaginae*, among women with different types of UI compared with healthy controls. Urinary microbiome has also been shown to differ depending on women's response to anticholinergic treatment response [112]. Further research is needed before the place of urine microbiome assessment in the clinical pathway for women with LUTS is fully defined.

Further information on the diagnostic efficacy of biomarkers in OAB can be found in section 4.1.3.3

3.9.1 ***Summary of evidence and recommendation for urinary biomarkers***

Summary of evidence	LE
There is insufficient evidence on the diagnostic accuracy and validity of urinary biomarkers for LUT disease in women.	3
Differences in the urinary microbiome have been found to be associated with different types of LUT dysfunction in women, including UI, and with different responses to treatment.	3

Recommendation	Strength rating
Do not routinely use urinary biomarkers or estimation of the urinary microbiome in the diagnosis and management of LUT disease in women.	Strong

4. DISEASE MANAGEMENT

4.1 Overactive bladder

4.1.1 ***Epidemiology, aetiology, pathophysiology***

Overactive bladder is defined by the ICS as "urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of UTI or other obvious pathology" [113].Overactive bladder is a chronic condition and can have debilitating effects on QoL. The hallmark urodynamic feature is DO, although this may not be demonstrated in a large proportion of OAB patients, which may partly be due to failure to reproduce symptoms during urodynamic assessment.

The EPidemiology of InContinence (EPIC) study was one of the largest population-based surveys of the prevalence of LUTS and OAB [114]. It was a cross-sectional telephone survey of adults aged > 18 years conducted in five countries, including Canada, Germany, Italy, Sweden and the UK. The study included > 19,000

participants and demonstrated an overall prevalence of OAB symptoms of 11.8% (10.8% in men and 12.8% in women). Other studies have reported prevalences of up to 30 to 40%, with rates generally increasing with age [5].

Various theories have been proposed to explain the pathophysiology of OAB, mainly relating to imbalances in inhibitory and excitatory neural pathways to the bladder and the urethra or sensitivity of bladder muscle receptors. However, no definite identifiable causes have been established.

*4.1.2 **Classification***

Overactive bladder is generally classified into wet and dry, based on the presence or absence of associated UI.

*4.1.3 **Diagnostic evaluation***

Evaluation of symptoms of OAB follows the general pathway of evaluation of women with LUTS.

4.1.3.1 Bladder diaries

Diaries are particularly helpful in establishing and quantifying symptoms of frequency, urgency and UI, and may be valuable in assessing change over time or response to treatment. Several observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [39-42]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance. Diary duration of three to seven days is routinely used in the literature.

4.1.3.2 Urodynamics

Urodynamics is essential in establishing the presence of DO, but its absence does not preclude diagnosis of OAB, which is based on symptoms alone.

A Cochrane review of seven RCTs showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery. However, there was no evidence that this influence on decision-making altered the clinical outcome of treatment [78]. A sub-analysis of an RCT comparing fesoterodine to placebo [85] showed that the urodynamic diagnosis of DO had no predictive value for treatment response.

4.1.3.3 Summary of evidence and recommendations regarding associated conditions

Summary of evidence	**LE**
Bladder diaries of three to seven days' duration may be helpful in quantifying symptoms of OAB, and assessing response to treatment.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a

Recommendations	**Strength rating**
Request that patients complete at least a three-day bladder diary at initial evaluation for overactive bladder (OAB).	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated OAB symptoms.	Strong

4.1.3.4 Urinary biomarkers

A SR and meta-analysis indicated that urinary NGF (standard mean difference [SMD]: 1.45; 95% confidence interval [CI]: 0.53-2.36), NGF/Cr ratio (SMD: 1.23; 95% CI: 0.67-1.78), BDNF/Cr ratio (SMD: 0.78; 95% CI: 0.006-1.50), and BDNF/Cr ratio (Risk ratio [RR]: 0.78; 95% CI: 0.006-1.50) were increased in female OAB patients compared to healthy controls, whereas no difference was found for the PGE2/Cr and ATP/Cr ratios [115]. The current data is inadequate to assess any other potential biomarkers, such as urinary malondialdehyde (UMDA), ATP, and cytokines, in the management of OAB in female patients. Further studies are needed to establish their potential as diagnostic and management tools in OAB women.

*4.1.4 **Disease management***

4.1.4.1 Conservative management

In clinical practice, it has long been the convention that non-surgical therapies are recommended first because they usually carry the lowest risk of harm. While this remains true for non-pharmacological conservative treatments [e.g., pelvic floor muscle training (PFMT)], increasing concerns regarding the adverse events of some pharmacological treatments used to treat LUTS (e.g., anticholinergic drugs), particularly regarding cognitive function, have emerged and patients should be fully counselled regarding this potential risk.

4.1.4.1.1 Addressing underlying disease

LUTS, especially in elderly patients, are associated with multiple comorbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease;
- general cognitive impairment;
- sleep disturbances, e.g., sleep apnoea;
- depression;
- metabolic syndrome.

It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently have more than one condition. However, if new treatment for any associated comorbidity has been linked (usually by the patient or carer) to a deteriration in LUTS then this should be reviewed by a health care practitioner (HCP).

One study involving middle-aged women with type 1 diabetes mellitus showed that 10% had UUI. The study showed no correlation between early intensive insulin treatment of type 1 diabetes mellitus vs. conventional insulin treatment and found no difference in the prevalence of UI in these patients later in their lives [113].

4.1.4.1.1.1 Summary of evidence and recommendation regarding associated conditions

Summary of evidence	**LE**
There is a lack of evidence that improving any associated comorbid condition improves OAB.	3

Recommendation	**Strength rating**
Review any new medication associated with the development or worsening of urinary incontinence.	Weak

4.1.4.1.2 Adjustment of other medication

Although LUTS are listed as adverse effects of many drugs, this mainly derives from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of LUTS as a primary outcome, or were powered to assess the occurrence of statistically significant LUTS or worsening rates against placebo. In most cases, it is therefore not possible to be sure that any drug causes OAB/LUTS.

A structured scoping review failed to identify any studies addressing whether adjustment of specific medications could alter existing symptoms of OAB.

4.1.4.1.2.1 Summary of evidence and recommendations for adjustment of non-LUTS medication

Summary of evidence	**LE**
There is little evidence that alteration of non-uroselective medications can cure or improve symptoms of OAB.	3

Recommendations	**Strength rating**
Take a history of current medication use from all patients with overactive bladder (OAB).	Strong
Review any new medication associated with the development or worsening of OAB symptoms.	Weak

4.1.4.1.3 Urinary containment

Urinary containment is important for people with OAB wet or UUI when active treatment does not cure the problem, is delayed, or when it is not available or not possible. Some individuals may prefer urinary containment rather than active treatment with its associated risks. Containment includes the use of absorbent pads, urinary catheters, external collection devices and intravaginal devices. Detailed literature summaries can be found in the current International Consultation on Urological Diseases (ICUD) monograph [8] and in a European Association of Urology Nurses guidance document [116].

A SR of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, while evidence that disposable pads were better than washable pads was inconsistent [117]. A series of three crossover RCTs examined performance of different pad designs for differing populations [118, 119]. For women with light UI, disposable insert pads (within washable pouch pants) were most effective. In adults with moderate/severe UI, disposable pull-up pants were more effective for women.

A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [120]. A SR of non-randomised studies found no differences in UTI outcome or UUT changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [121].

Catheter-related bladder discomfort may be significant in women. Anticholinergics have been proposed to prevent or reduce this issue, but most of the evidence comes from clinical trials in the postoperative period, and the results are controversial [122-125]. One retrospective study including 40 women (most of them neurogenic) with long-term bladder catheters found intravesical botulinum toxin injections helped to prevent bladder pain and discomfort and catheter bypass/leakage. Patients reported an improvement in QoL and a significant 83% reduction in urine leakage [126].

Clean intermittent self-catheterisation (CISC) is the most commonly used therapy to manage high PVR volume and urinary retention [116]. It reduces the risk of complications such as UTI, UUT deterioration, bladder stones and overflow UI etc. It has not yet been established whether the incidence of UTI, other complications and user satisfaction are affected by either sterile or clean intermittent catheterisation (IC), coated or uncoated catheters or by any other strategy [127]. The use of hydrophilic catheters may be associated with a lower rate of UTI, but further evidence is needed, as current data comes from neurogenic patients [128]. The average frequency of catheterisation is four to six times per day [129] and the catheter sizes most often used are 12–16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [129]. Frequency of catheterisation needs to be based on individual need and capability, to prevent chronic and repeated over-filling of the bladder [130]. Thorough counselling regarding techniques, frequency, equipment and adverse effects of CISC should be given to all potential patients in line with good medical practice.

For people using CISC, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [131]. However, a recent narrative review suggests that, in certain populations, single-use catheters may reduce urethral trauma and UTI [132]. A Cochrane review summarising five trials comparing bladder washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [133].

A further Cochrane review summarising eight trials of whether antibiotic prophylaxis was beneficial for adults using CISC or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [134]. A multicentre RCT from the UK reported that prophylaxis was well-tolerated but development of antibiotic resistance was a concern [135].

4.1.4.1.3.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	**LE**
Pads are effective in containing urine.	1b
Antibiotic prophylaxis may help reduce incidence of UTI in patients who self-catheterise or have an indwelling catheter, but at the cost of increasing antimicrobial resistance.	1a

Recommendations	**Strength rating**
Ensure that women with overactive bladder (OAB) and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of wet OAB, either for temporary symptom control or when other treatments are not planned.	Strong
Offer prophylactic antibiotics to patients with recurrent UTI who perform clean intermittent catheterisation, after discussion regarding the risk of increasing antimicrobial resistance.	Strong

4.1.4.1.4 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity, regulation of bowel habit and fluid intake. Modification of these factors may improve symptoms of OAB.

4.1.4.1.4.1 Caffeine intake

Many drinks contain caffeine, particularly coffee, tea and cola. Conflicting epidemiological evidence of urinary symptoms being aggravated by caffeine intake has focused on whether caffeine reduction improves LUTS [136, 137]. A scoping review of fourteen interventional and twelve observational studies reported that reduction in caffeine intake may reduce symptoms of urgency, but the certainty of evidence was low, with significant heterogeneity in study populations [138].

4.1.4.1.4.2 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with OAB to relieve symptoms. Any advice on fluid intake given by HCPs should be based on 24-hour fluid intake and urine output measurements as retrieved from the bladder diary. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that an abnormally low or high 24-hour urine output should be investigated. The few RCTs that have been published provide inconsistent evidence [139-141]. In most studies, the instructions for fluid intake were individualised and it was difficult to assess participant adherence. All available studies were in women. An RCT showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI [141]. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving anticholinergics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [142]. Patients should be warned of the potential consequences of fluid restriction such as worsening of constipation or development of UTI.

4.1.4.1.4.3 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for LUTS in many epidemiological studies [143, 144]. There is evidence that the prevalence of both UUI and SUI increases proportionately with body mass index [145]. However, the evidence base largely relates to obesity and SUI rather than UUI and OAB. Therefore, no definite inference can be drawn between obesity and the prevalence of OAB.

4.1.4.1.4.4 Smoking

Smoking cessation is a general public health measure and has been shown to be weakly associated with improving urgency, frequency and UI [146, 147]. The effect of smoking cessation on LUTS was described as uncertain in a health technology assessment review [148].

4.1.4.1.4.5 Summary of evidence and recommendations for lifestyle interventions

Summary of evidence	**LE**
Reduction of caffeine intake may reduce symptoms of frequency and urgency.	2
Addition of personalised fluid intake advice to pharmacotherapy provides no additional benefit in patients with OAB.	2
Reduction in fluid intake by 25% may help improve symptoms of OAB but not UI.	1b
Obesity is a risk factor for UI in women, but the relationship to other OAB symptoms remains unclear.	1b
There is weak evidence that smoking cessation improves symptoms of OAB.	3

Recommendations	**Strength rating**
Encourage overweight and obese adults with overactive bladder (OAB)/urinary incontinence to lose weight and maintain weight loss.	Strong
Advise adults with OAB that reducing caffeine intake may improve symptoms of urgency and frequency, but not incontinence.	Strong
Review type and amount of fluid intake in patients with OAB.	Weak
Provide smoking cessation strategies to patients with OAB who smoke.	Strong

4.1.4.1.5 Behavioural and physical therapies

Approaches include bladder training (BT) and PFMT. Almost always in clinical practice, these are introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package, especially for adherence to training.

A SR on cognitive components of behavioural therapies for OAB concluded that they were neither well described nor rationalized. Behavioural therapy that includes a cognitive component shows promise for OAB

treatment, but its relative importance has not been evaluated nor rigorously studied. Cognitive strategies include mental distraction (the most common), relaxation and mindfulness practices [149].

4.1.4.1.5.1 Prompted voiding and timed voiding

The term 'prompted voiding' implies that carers, rather than the patient, initiate the patient going to void with the aim of preventing or reducing UI. This applies largely to an assisted care setting. One SR (including nine RCTs), comparing prompted voiding in comparison to standard care, suggested evidence of short-term benefit for management of UI, but longer-term effects are unknown [150].

Timed voiding is defined as fixed, predetermined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs, finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [151].

4.1.4.1.5.2 Bladder training

Bladder training is a programme of patient education along with a scheduled voiding regimen with gradually increasing intervals. Specific goals are to correct faulty patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes and restore patient confidence in controlling bladder function. The ideal form or intensity of a BT programme for OAB/UI is unclear. It is also unclear whether or not BT can prevent development of OAB/UI.

There have been three SRs on the effect of BT compared to standard care confirming that BT is more effective than no treatment in improving UUI [67, 148, 152]. The addition of BT to anticholinergic therapy did not improve UUI compared to anticholinergics alone but it did improve frequency and nocturia [153]. A review identified seven RCTs in which BT was compared to drug therapy alone and only showed a benefit for oxybutynin for cure or improvement of UUI [153].

4.1.4.1.5.3 Pelvic floor muscle training

An immediate effect of PFM contraction is simultaneous inhibition of urgency, detrusor contraction and incontinence [154]. Intensive and regular strength training of the PFMs over time increases both PFM contraction strength and endurance, and changes the morphology of the pelvic floor, which may yield more effective inhibition of the detrusor and help to stabilize the proximal urethra and improve urethral function. There is a lack of basic and mechanistic studies to confirm that change in pelvic floor morphology improves OAB symptoms.

A SR of eleven RCTs [155] including women with OAB compared the efficacy of PFMT vs. inactive control, usual care, other lifestyle modification or other intervention. Pelvic floor muscle training significantly reduced OAB symptoms (frequency and UUI) in five RCTs, while the remaining six reported no significant difference. Significant heterogeneity in protocols precluded meaningful comparisons.

4.1.4.1.5.4 Electrical stimulation

The methods of delivery of electrical stimulation (ES) vary considerably. Electrical stimulation of the PFM can also be combined with other forms of conservative therapy; e.g., PFMT with and without biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their PFMs and in patients with OAB and UUI with the aim of inhibiting detrusor contraction. There is, however, a lack of basic and mechanistic studies to confirm this theory.

A SR of the effect of ES included 51 trials with 3,443 adults with OAB symptoms [156], with quality of evidence ranging from very low to moderate. Moderate-quality evidence suggests that ES is more likely to improve OAB symptoms compared to sham control, no treatment or placebo. Moderate-quality evidence suggests that ES is more likely to improve OAB symptoms compared to anticholinergic therapy. There is insufficient evidence for comparisons with PFMT and between different types of ES.

4.1.4.1.5.5 Acupuncture

A SR with meta-analysis of ten RCTs including 794 patients (590 women) reported that acupuncture might have an effect in reducing OAB symptoms compared to sham treatment [157]. The studies were of low quality and compared electro-acupuncture vs. sham acupuncture, or electro-acupuncture plus tolterodine vs. tolterodine alone. An up-to date SR from the Cochrane collaboration is planned for 2022 [158].

4.1.4.1.5.6 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2–S4 sacral plexus. Stimulation is percutaneous with a fine (34-G) needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS) that delivers

stimulation via surface electrodes that do not penetrate the skin. Treatment cycles typically consist of twelve weekly treatments of 30 minutes.

4.1.4.1.5.6.1 Percutaneous posterior tibial nerve stimulation

The reviewed studies included a SR, two twelve-week RCTs of P-PTNS compared with sham treatment [159-161], one comparing PTNS to tolterodine, and a three-year extension trial utilising a maintenance protocol in patients with UUI [162, 163]. The results of studies of PTNS in women with refractory UUI are consistent. These results suggest that PTNS improves UUI in women who do not have adequate improvement or cannot tolerate anti-muscarinic therapy. Improvements in voiding frequency, nocturia, urgency, incontinence episodes, cystometric capacity and compliance were described in the SR [161]. The major complication was pain at the puncture site, but the incidence was low. However, there was no good evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women.

4.1.4.1.5.6.2 Transcutaneous posterior tibial nerve stimulation

A small RCT compared T-PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [164]. Women in the T-TPNS group were more likely to achieve improvement at the end of therapy. A SR of thirteen trials (ten RCTs and three cohort studies) compared the efficacy of T-PTNS (duration four to twelve weeks) with sham treatment, anticholinergics, and exercise in treatment of adults with OAB symptoms [165]. Of note, the populations were adult women and men, and some studies included patients with neurogenic OAB. Meta-analysis was possible in two RCTs comparing T-PTNS with sham treatment, and revealed mean reduction in total international consultation on incontinence modular questionnaire (ICIQ) Urinary Incontinence Short Form (ICIQ-UI SF) associated with T-PTNS of –3.79 points.

A SR with meta-analysis including three RCTs (two RCTs comparing P-PTNS with solifenacin and one RCT comparing T-PTNS with oxybutynin) found PTNS to be more effective than anticholinergics in improving UUI in women with OAB on short-term follow-up of ≤ 12 weeks (mean difference [MD]: -0.67; 95% CI: -1.31 to -0.02). The certainity of evidence was low to moderate. However, the meta-analysis revealed no statistically significant difference between PTNS and anticholinergics in improvement of mean symptoms scores on validated questionnaires, frequency, or urgency episodes [11]. Adding anticholinergics to PTNS added no statistically significant value to improvement of any of OAB symptoms than PTNS alone [166].

A small RCT compared BT alone, BT plus P-PTNS and BT plus T-PTNS in women with idiopathic OAB. Both P-PTNS and T-PTNS were more effective than BT alone. These two tibial nerve stimulation methods had similar clinical efficacy but with slight differences: TTNS had shorter preparation time, less discomfort level and higher patient satisfaction than PTNS [166].

4.1.4.1.5.7 Summary of evidence and recommendations for behavioural and physical therapies

Summary of evidence	**LE**
Bladder training is effective for improvement of UUI in women.	1b
Combination of BT with anticholinergic drugs does not result in greater improvement of UUI, but may improve frequency and nocturia.	1b
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
Pelvic floor muscle training may improve symptoms of frequency and incontinence in women.	1b
Electrical stimulation may improve symptoms of OAB in some women, but the type and mode of delivery of ES remains variable and poorly standardised.	1a
Percutaneous-posterior tibial nerve stimulation appears effective in the short-term for improving UUI in women who have had no benefit from anticholinergic medication but in general is not curative.	2b
A maintenance programme of P-PTNS has been shown to be effective for up to 3 years.	1b
Percutaneous-PTNS has comparable effectiveness to tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
Transcutaneous-PTNS appears to be effective in reducing OAB symptoms compared to sham treatment.	1a

Recommendations	**Strength rating**
Offer prompted voiding for adults with overactive bladder (OAB) who are cognitively impaired.	Strong
Offer bladder training as first-line therapy to adults with OAB/UUI.	Strong
Ensure that pelvic floor muscle training programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for improvement of OAB/UUI in women who have not benefitted from anticholinergic medication.	Strong

4.1.4.2 Pharmacological management

4.1.4.2.1 Anticholinergic drugs

Anticholinergic (antimuscarinic) drugs are currently the mainstay of treatment for OAB. They differ in their pharmacological profiles, such as muscarinic receptor affinity and other modes of action and in their pharmacokinetic properties, such as lipid solubility and half-life.

The evaluation of cure or improvement of OAB is made harder by the lack of standard definitions. In general, a SR noted that the overall treatment effect of drugs is usually small but larger than that of placebo. Some RCTs have UI as an outcome rather than UUI. Dry mouth is the commonest adverse effect, although constipation, blurred vision, fatigue and cognitive dysfunction may occur with anticholinergic drugs [152].

Immediate-release (IR) anticholinergic preparations provide maximum dosage flexibility, including an off-label on-demand use. Immediate-release drugs have a greater risk of adverse effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system and gel developed for oxybutynin provide alternative formulations.

Seven SRs of individual anticholinergic drugs vs. placebo have been reviewed [152, 167-172]. Most studies included patients with a mean age of 55–60 years. The evidence reviewed was consistent, indicating that ER and IR formulations of anticholinergics offer clinically significant short-term improvement of OAB compared to placebo. On balance, IR formulations tend to be associated with more adverse effects compared to ER formulations [171].

A network meta-analysis of 128 RCTs comparing anticholinergics with placebo or other anticholinergics revealed that all anticholinergics, except imidafenacin, showed significant cure or improvement rates for OAB symptoms in both sexes [173].

Cure of UUI is deemed to be the most important outcome measure. Table 1 shows a summary of the findings from SRs [152]. Every drug for which cure of UUI was available showed superiority compared to placebo, but the absolute size of the effect was small. There is limited evidence that patients who do not respond to first-line anticholinergic treatment respond to a higher dose or a different anticholinergic agent [174, 175]. Risk of adverse events is often represented by trial withdrawal, although this does not reflect clinical practice. The cure rates for darifenacin were not included in the US Agency for Healthcare Research and Quality (AHRQ) review. Continence rates were 29–33% for darifenacin compared to 17–18% for placebo [152]. Transdermal oxybutynin showed a significant improvement compared with placebo and other oral formulations in the number of incontinence episodes and micturitions per day but cure of UI was not reported as an outcome [152].

Oxybutynin topical gel was superior to placebo for improvement of UUI, with a higher proportion of participants being cured [152, 176].

Table 1: Summary of cure and discontinuation rates of anticholinergic drugs from RCTs [152]

Drug	**No. of studies**	**No. of patients**	**RR (95% CI) (of curing UI)**	**NNT (95% CI) (to achieve one cure of UI)**
Cure of incontinence				
Fesoterodine	2	2465	1.3 (1.1–1.5)	8 (5–17)
Oxybutynin (includes IR)	4	992	1.7 (1.3–2.1)	9 (6–16)
Propiverine (includes IR)	2	691	1.4 (1.2–1.7)	6 (4–12)
Solifenacin	5	304	1.5 (1.4–1.6)	9 (6–17)
Tolterodine (includes IR)	4	3404	1.2 (1.1–1.4)	12 (8–25)
Trospium (includes IR)	4	2677	1.7 (1.5–2.0)	9 (7–12)
Discontinuation due to adverse events				
			RR (95% CI) (of discontinuation)	**NNT (95% CI) (for one discontinuation)**
Darifenacin	7	3138	1.2 (0.8–1.8)	
Fesoterodine	4	4433	2.0 (1.3–3.1)	33 (18–102)
Oxybutynin (includes IR)	5	1483	1.7 (1.1–2.5)	16 (8–86)
Propiverine (includes IR)	2	1401	2.6 (1.4–5)	29 (16–77)

Solifenacin	7	9080	1.3 (1.1–1.7)	78 (39–823)
Tolterodine (includes IR)	10	4466	1.0 (0.6–1.7)	
Trospium (includes IR)	6	3936	1.5 (1.1–1.9)	56 (30–228)

CI = confidence interval; IR = immediate release; NNT = number to treat; RR = relative risk; UI = urinary incontinence.

4.1.4.2.1.1 Comparison of different anticholinergic agents

Head-to-head comparison trials of the efficacy and adverse effects of different anticholinergic agents are of interest for decision-making.

A network meta-analysis revealed no clear best anticholinergic preparation for cure or improvement [173]. Darifenacin (40%), tolterodine IR and oxybutynin ER (13% each) appeared to score highest in indirect comparisons. Fesoterodine and oxybutynin IR were more effective than oxybutynin (transdermal) and tolterodine ER. There were no clinically significant differences between anticholinergics for voiding and UI outcomes.

Another network meta-analysis of 53 RCTs compared the efficacy and tolerability of solifenacin 5 mg with other oral anticholinergics in the treatment of adults with OAB symptoms [177]. Solifenacin 5 mg/day was significantly more effective than tolterodine 4 mg/day for reducing UUI episodes, but significantly less effective than solifenacin 10 mg/day for reducing micturition episodes. Solifenacin 5 mg/day showed significantly lower risk of dry mouth compared with other anticholinergics. There were no significant differences for the risk of blurred vision or constipation.

It is notable that nearly all the primary studies in this category were industry sponsored. Upward dose titration is often included in the protocol for the experimental arm but not for the comparator arm. In general, these studies have been designed to achieve regulatory approval. They have short treatment durations (twelve weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real-life practice is therefore debatable. Most trials were of low or moderate quality [169]. The 2012 AHRQ review included a specific section addressing comparisons of anticholinergic drugs (Table 1).

No single anticholinergic agent improved QoL more than another [169]. Dry mouth is the most prevalent adverse effect. Extended release formulations of short- and longer-acting drugs are associated with lower rates of dry mouth than IR preparations are [169, 178]. Oxybutynin IR shows higher rates of dry mouth than tolterodine IR and trospium IR show, but lower rates of dry mouth than darifenacin, 15 mg daily [169, 178]. Overall, oxybutynin ER causes higher rates of dry mouth than tolterodine ER does, although the incidence of moderate or severe dry mouth is similar. Transdermal oxybutynin has a lower rate of dry mouth than oxybutynin IR and tolterodine ER have, but an overall higher rate of withdrawal due to adverse skin reactions [169]. Solifenacin 10 mg daily has higher rates of dry mouth than tolterodine ER [169]. Fesoterodine 8 mg daily has a higher rate of dry mouth than tolterodine 4 mg daily [179-181]. Similar discontinuation rates have been observed, irrespective of differences in the occurrence of dry mouth.

4.1.4.2.1.2 Anticholinergic drugs versus conservative treatment

The choice of pharmacologic vs. conservative treatment of OAB patients is an important question. More than 100 RCTs and high-quality reviews are available [153, 169, 170, 182-184]. Most of these were independent studies. The main focus of the reviews was to compare the different drugs used to treat UUI. A U.S. health technology assessment [182] found that trials were of a low or moderate quality.

The combination of BT and solifenacin in female patients with OAB confers no additional benefit in terms of continence compared with solifenacin monotherapy [185]. A recent Cochrane review on the benefit of adding PFMT to other active treatments of UI in women showed insufficient evidence of any benefit in adding PFMT to drug treatment [186].

One RCT reported a similar improvement in subjective parameters with T-PTNS or oxybutynin [187]. One study compared tolterodine ER to transvaginal/anal ES in women with OAB symptoms and/or UUI without demonstrating any differences in UI outcomes [188].

A SR with meta-analysis included RCTs combining anticholinergics with various non-invasive modalities including pregabalin, topical estrogenic, and physiotherapy. The review showed that these combinations were associated with significantly higher improvement in mean symptoms score on validated questionnaires

(6 RCTs, MD: 0.55; 95% CI: 0.16-0.95), urgency episodes (4 RCTs, MD: 0.68; 95% CI: 0.04-1.32) and UUI episodes (5 RCTs, MD: 1.18; 95% CI 0.18-2.17). The quality of evidence was low to moderate [11].

A SR with meta-analysis of 57 RCTs assessed the role of placebo in patients with OAB, it showed that placebo had age-dependent statistically significant effect on improvement of OAB symptoms including urgency daily episodes (MD: -0.51; 95% CI: -0.60 to -0.43) and UUI episodes (MD: -0.05; 95% CI: -0.61 to -0.39) [189]. The authors concluded that placebo response is non-negligible and is of importance in RCTs as a control arm. The same group published a SR with meta-analysis of data retrieved from 57 RCTs on the nocebo effect of pharmacotherapy in patients with OAB (up to 80% females). They reported dry mouth as the most commen reported adverse event with mean rate of 4.9% (95% CI: 0.042 to -0.057) followed by constipation 2.6%, (95% CI: 0.022 to 0.031), the authors concluded that HCPs should appreciate the possible positive and negative patient expectation regarding pharmacotherapy for OAB in order to optimise the individual outcomes [190].

4.1.4.2.1.3 Anticholinergic drugs: adherence and persistence

Most studies on anticholinergic medication are short-term (twelve weeks). Adherence in clinical trials is considered to be higher than in clinical practice [191]. This topic has been reviewed for the development of a previous version of these guidelines [192]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at twelve months, and particularly high (68–95%) for oxybutynin. Two open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at two years of 49–84% [193, 194].

Five articles reported median days to discontinuation, but follow-up periods varied from < 30 up to 50 days [195-199]. In a military health system where free medication was provided, the median time to discontinuation extended to 273 days [196].

Data on adherence/persistence from open-label extension populations are questionable as it could be argued that these patients are self-selected on the basis of their compliance. A longitudinal disease analyser database study has indicated an increasing discontinuation rate, following treatment with anticholinergics, from 74.8% at one year to 87% at three years [200].

Several of the RCTs tried to identify the factors associated with low/lower adherence or persistence of anticholinergics. These were identified as:

- low level of efficacy (41.3%);
- adverse events (22.4%);
- cost (18.7%), although higher adherence rates were observed when drugs were provided at no cost to patients [196].

Other reasons for poor adherence included:

- immediate release formulations (lower persistence compared with ER formulations);
- age (lower persistence among younger adults);
- unrealistic expectations of treatment;
- gender distribution (better adherence/persistence in female patients);
- ethnic group (African–Americans and other ethnic minorities are more likely to discontinue or switch treatment).

4.1.4.2.1.4 Summary of evidence and recommendations for anticholinergic drugs

Summary of evidence	**LE**
No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI.	1a
Higher doses of anticholinergic drugs are more effective to improve OAB symptoms, but exhibit a higher risk of adverse effects.	1a
Once daily (ER) formulations are associated with lower rates of adverse events compared to IR preparations.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral anticholinergic drugs are, but has a high rate of withdrawal due to skin reactions.	1b
There is no consistent evidence to show superiority of drug therapy over conservative therapy for treatment of OAB.	1b
Behavioural treatment may have higher patient satisfaction rates than drug treatment.	1b
There is insufficient evidence as to the benefit of adding PFMT to drug treatment for OAB.	1b

Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2a
Most patients will stop anticholinergic agents within the first three months.	2a

Recommendations	**Strength rating**
Offer anticholineric drugs to woman with overactive bladder (OAB) who fail conservative treatment.	Strong
Consider extended release formulations of anticholinergic drugs whenever possible.	Strong
If an anticholinergic treatment proves ineffective, consider dose escalation, offering an alternative anticholinergic formulation, or the use of mirabegron (alone or in combination with an anticholinergic).	Strong
Encourage early review (of efficacy and adverse effects) of patients on anticholinergic medication for OAB.	Strong

4.1.4.2.2 Beta-3 agonists

Beta-3 adrenoceptors are the predominant beta receptors expressed on detrusor smooth muscle cells and their stimulation is thought to induce detrusor relaxation. Mirabegron was the first clinically available beta-3 agonist. Vibegron is another beta-3 agonist commercially available in some countries.

Mirabegron has undergone evaluation in industry-sponsored phase II and III trials [201-204]. Three SRs assessing the clinical effectiveness of mirabegron [201, 202, 205] reported that mirabegron at doses of 25, 50 and 100 mg results in significantly greater reduction in UI episodes, urgency episodes and micturition frequency than placebo, with no difference in the rate of common adverse events [202]. The dry rates in most of these trials are 35–40% for placebo and 43–50% for mirabegron. In all trials the significant differences were consistent only for improvement but not for cure of UI. Similar improvements in the frequency of UI episodes and micturition frequency were found whether or not patients had previously tried anticholinergic agents. One SR showed that mirabegron is as efficacious as most anticholinergics in reducing UUI episodes [206]. One SR [207] assessed the outcomes of mirabegron in women with OAB. It included seven RCTs, three non-RCTs and eleven observational studies. The review reported no statistical difference between mirabegron and anticholinergics in decreasing OAB symptoms on voiding diaries and symptom questionnaires on short-term follow-up (up to twelve weeks). However, at one year follow-up, there was statistically significant decrease in OAB symptoms (MD: -0.35; 95% CI: -0.51 to -0.19) in favour of mirabegron.

The most common adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to that with placebo [201, 204, 208].

A SR with meta-analysis of data pooled from three RCTs comparing vibegron (75 mg or 100 mg) with placebo in 2120 patients with OAB revealed significant improvement of urgency episodes (MD: -0.77; 95% CI: -1.03 to -0.52) and UUI episodes (MD: -0.45; 95% CI: -0.64 to -0.34) and mean voided volume (MD: 22.2; 95% CI: 17.36 to 27.7) associated with vibegron [209]. The review also reported that vibegron showed a favourable safety profile. Another SR that included three high-quality RCTs compared vibegron with anticholinergic monotherapy (imidacine and tolterodine) concluding similar efficacy in terms of improvements in mean number of micturitions, urgency and UUI episodes, but with less dry mouth in vibegron groups [210].

In a twelve-month, active-controlled RCT of mirabegron 50/100 mg vs. tolterodine ER 4 mg, improvement in efficacy at twelve weeks was sustained at twelve months in all groups. The reported dry rates at twelve months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [208]. *Post hoc* analyses of RCTs showed that clinical improvement in OAB severity translates into improvement in health-related quality of life (HRQoL), and efficacy is maintained in patients with more severe UI [211, 212]. No risk of QTc prolongation [213] and no raised intraocular pressure [214] were observed up to the 100 mg dose; however, patients with uncontrolled hypertension or cardiac arrhythmia were excluded from these trials. There is no significant difference in the rate of adverse effects at different doses of mirabegron [208]. Patients on concurrent medication (e.g., metoprolol) should be counselled that, due to common metabolic pathways, their drug dose may need to be adjusted. In the case of patients taking metoprolol, blood pressure should be monitored after starting mirabegron and, if necessary, the metoprolol dose may need to be changed.

Equivalent adherence was observed for tolterodine and mirabegron at twelve months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [208]. In mirabegron-treated patients, improvement in objective outcome measures correlates directly with clinically relevant

PROMs (Overactive Bladder questionnaire and Patient Perception of Bladder Condition) [211, 215]. Data from a large Canadian Private Drug Plan database suggest a higher adherence rate for mirabegron compared to anticholinergics [216].

An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg demonstrated that combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [217].

4.1.4.2.2.1 Summary of evidence and recommendation for beta-3 agonists.

Summary of evidence	LE
Mirabegron and vibegron are better than placebo and as efficacious as anticholinergics for improvement of OAB/UUI symptoms.	1a
Adverse event rates with mirabegron and vibegron are similar to those of placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron rather than dose escalation of solifenacin.	1b

Recommendation	Strength rating
Offer beta-3 agonists as an alternative to anticholinergics to women with OAB who fail conservative treatment.	Strong

4.1.4.2.3 Anticholinergics and beta-3 agonists: elderly patients and cognition

Trials have been conducted in elderly patients with OAB. Considerations in this patient group include the multifactorial aetiology of OAB, comorbidities such as cognitive impairment, the effect of concomitant medications, and the risk of adverse events. The effects of anticholinergic agents on cognition have been studied in more detail.

Systematic reviews have included sections on the efficacy and safety of anticholinergics in elderly patients [152, 169]. A 2012 SR found inconclusive evidence of the impact of anticholinergics on cognition [218].

Two recent longitudinal cohort studies in patients using anticholinergic drugs showed deterioration in cognitive function, alteration in central nervous system metabolism and an association with brain atrophy [219, 220]. As most of the study periods are short (four to twelve weeks), the long-term impact of anticholinergic agents specifically approved for OAB treatment on specific patient cohorts are poorly understood [221-224].

- *Oxybutynin:* There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [221, 223, 225, 226]. One RCT with oxybutynin topical gel focused on cognitive and psychomotor function after one week of treatment showed no clinically meaningful effect on recent memory or other cognitive functions in healthy elderly adults [226]. Another retrospective study did not show cognitive impairment after four weeks of treatment with transdermal oxybutynin [223]. Recent evidence has emerged from a prospective cohort study showing cumulative cognitive deterioration associated with prolonged use (mean follow-up 7.3 years) of anticholinergic medication including oxybutynin [219]. Another prospective cohort study including 376 nursing residents aged 65 and older taking oxybutynin and tolterodine showed a decline in activity of daily living after a median follow-up of 141 days, in spite of concomitant treatment with cholinesterase inhibitors [227].

- *Solifenacin:* One pooled analysis [228] showed that solifenacin did not increase cognitive impairment in elderly patients. No age-related differences in the pharmacokinetics of solifenacin in different age groups were found, although more frequent adverse events in patients aged > 80 years were observed. No cognitive effect on healthy elderly volunteers was shown [229]. In a sub-analysis of a large trial, solifenacin 5–10 mg improved symptoms and QoL in people aged ≥ 75 years who had not responded to tolterodine [230]. In patients with mild cognitive impairment, aged ≥ 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most adverse effects compared to oxybutynin IR [226, 231].

- *Tolterodine:* No change in efficacy or adverse effects related to age has been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [221]. Two RCTs in elderly patients found similar efficacy and adverse effect profile to those in younger patients [232-235].

Post hoc analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [236]. Duration of the RCTs was short (twelve weeks).

- *Darifenacin:* Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that, compared with placebo, darifenacin was effective with no risk of cognitive change, measured as memory scanning tests [237, 238]. Another study on darifenacin and oxybutynin ER in elderly people concluded that the two agents had similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [223].

- *Trospium chloride:* Trospium does not appear to cross the blood–brain barrier in healthy individuals due to its molecular characteristics (quaternary amine structure and hydrophilic properties). Two studies in healthy volunteers using electroencephalography showed no effect from trospium, while tolterodine caused occasional changes and oxybutynin caused consistent changes [239, 240]. No evidence as to the comparative efficacy and adverse effect profiles of trospium in different age groups are available. However, there is some evidence that trospium does not impair cognitive function in Alzheimer's disease patients if combined with cholinesterase inhibitors in a six month period [224], or in non-cognitively impaired patients over shorter periods (twelve weeks) [241] and that it is effective compared to placebo in the elderly [242].

- *Fesoterodine:* Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of 8 mg but not 4 mg dose in patients aged > 75 years [193]. Adherence was lower in patients aged > 75 years but effects on mental status were not reported [181, 193, 243]. A more recent RCT showed efficacy of fesoterodine in vulnerable elderly people with no differences in cognitive function at twelve weeks [244].

- *Mirabegron:* Analysis of pooled data from three RCTs showed efficacy and safety of mirabegron in elderly patients [245].

4.1.4.2.3.1 Applicability of evidence to the general elderly population

It is not clear how much the data from pooled and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of anticholinergic adverse effects may be the most helpful [246]. When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [247]. No consensus exists as to the best mental function test to detect changes in cognition [227, 248].

4.1.4.2.3.2 Anticholinergic burden

Several drugs have anticholinergic effects and, if another anticholinergic drugs are prescribed, possible cumulative effects on cognition should be considered. Lists of drugs with anticholinergic properties are available from several sources [249].

No studies were identified specifically in older people with LUTS, but evidence is available from observational cohort studies relating to the risk in a general population of older people.

Two SRs of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [250, 251]. Longitudinal studies in older people over two to four years have found increased rates of cognitive decline in patients on anticholinergics or drugs with anticholinergic effects [219, 220, 252, 253]. It is unclear whether there is a direct correlation between cognitive dysfunction caused by medication and the long-term risk of development of dementia.

4.1.4.2.3.3 Summary of evidence and additional recommendations for use of anticholinergic drugs in elderly patients

Summary of evidence	**LE**
Anticholinergic drugs are effective in elderly women suffering from OAB/UUI.	1b
Mirabegron has been shown to be efficacious and safe in elderly women suffering from OAB.	1b
In older women the cognitive impact of drugs with anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly women.	2
Darifenacin, fesoterodine, solifenacin and trospium have not been shown to cause cognitive dysfunction in elderly women in short-term studies.	1b

Recommendations	Strength rating
Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction.	Strong
Assess anticholinergic burden and associated comorbidity in women being considered for anticholinergic therapy for overactive bladder syndrome.	Weak

4.1.4.2.4 Oestrogens

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women. Available evidence is related mainly to SUI, and although some reviews include participants with UUI, it is difficult to generalise the results to women with predominantly OAB/UUI.

The association of LUTS with genitourinary syndrome of menopause (GSM) should be considered [254]. Genitourinary syndrome of menopause (GSM) is a new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina and LUT. These include mucosal pallor/erythema, loss of vaginal rugae, tissue fragility/fissures, vaginal petechiae, urethral mucosal prolapse, introital retraction and vaginal dryness. There is evidence from a SR to suggest benefit from vaginal oestrogen therapy in GSM [255]. All vaginal oestrogens demonstrated superiority in objective and subjective end points of GSM compared with placebo. Only some trials demonstrated superiority vs. placebo in urogenital symptoms (UI, recurrent UTI, urgency and frequency). No significant difference was observed between various doses and dosage forms of vaginal oestrogen products. Vaginal oestrogen showed superiority over vaginal lubricants and moisturisers for the improvement of objective clinical end points of vulvovaginal atrophy but not for subjective end points [255].

Available evidence suggests that vaginal treatment with oestradiol and oestriol is not associated with increased risk of thromboembolism, endometrial hypertrophy, and breast cancer that is seen with systemic administration [256-258].

4.1.4.2.4.1 Summary of evidence and recommendation for oestrogen therapy

Summary of evidence	LE
Vaginal oestrogen therapy may improve symptoms associated with GSM, of which OAB may be a component.	1a

Recommendation	Strength rating
Offer vaginal oestrogen therapy to women with LUTS and associated symptoms.	Weak

4.1.4.2.5 Placebo

Placebo has a clear effect on the improvement of OAB signs and symptoms, and the overall placebo responses in various outcomes studied are statistically significant and, for some of the outcomes, possibly clinically significant. A recent SR including 57 studies with 12901 patients showed a standardised MD of -0.45 (95% CI: -0.51 to -0.40; $p < 0.001$) for daily micturition episodes, -0.33 (95% CI: -0.42 to -0.24; $p < 0.001$) for daily nocturia episodes, -0.46 (95% CI: -0.55 to -0.37; $p < 0.001$) for UUI episodes, -0.50 (95% CI: -0.61 to -0.39; $p < 0.001$) for daily urgency episodes, -0.51 (95% CI: -0.60 to -0.43; $p < 0.001$) for daily incontinence episodes, and 0.25 (95% CI: 0.211–0.290; $p < 0.001$) for volume voided per micturition [189]. The placebo response seems to be non-negligible in OAB, supporting the requirement for placebo control in RCTs.

4.1.4.3 Surgical management

4.1.4.3.1 Bladder wall injection of botulinum toxin A

Onabotulinum toxin A (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both sexes [259, 260]. Surgeons should be aware that other doses of onabotA and other formulations of botulinumtoxin A, abobotulinumtoxin A and incobotulinumtoxin A, are not licensed for use in OAB/UUI. Doses for onabotA are not transposable to the other brands of botulinumtoxin A. The continued efficacy of repeat injections is usual, but discontinuation rates may be high [261, 262]. The most important adverse events related to onabotA 100U injection detected in the regulatory trials were UTI and an increase in PVR volume that may require CISC [263].

Following a dose-ranging study in which 100 U onabotA was established as the optimum dose, a phase III trial randomised (1:1) the same group of 557 OAB-wet patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline, the population had on average > 5 episodes of UUI, ~12 micturitions per day and a small PVR volume. At week twelve, in patients treated with onabotA, UUI episodes/day were halved and the number of micturitions/day reduced by > 2. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [263]. Rates of urinary retention were not reported in SRs, and a Cochrane review reported no significant difference in PVR volume between the onabotA and placebo groups [264].

Quality of life was substantially improved in the onabotA arm, as shown by the > 2.5 times improvement in Incontinence Quality of Life Questionaire (I-QOL) scores compared to baseline. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in elderly and frail elderly people [265], although the success rate might be lower and the PVR volume (> 150 ml) higher in this group.

The median time to request retreatment in the pooled analysis of the two RCTs was 24 weeks [260, 263]. Follow-up over 3.5 years showed consistent or increasing duration of effect for each subsequent treatment, with a median of 7.5 months. Considerable differences were noted in patient outcomes on secondary analysis [266].

An RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed similar rates of improvement in UUI over the course of 6 months [267]. However, patients receiving onabotA were not only more likely to have cure of UUI (27% vs. 13%), but also had higher rates of urinary retention during the initial 2 months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking anticholinergics were more likely to have dry mouth. These results are further strengthened by a 2017 SR and network meta-analysis including 65 RCTs of onabotulinum toxin A vs. oral therapies (anticholinergics and mirabegron) for OAB at twelve weeks [268]. This review reported that patients receiving onabotulinum toxinA had the greatest reduction in UUI episodes, urgency episodes, micturition frequency and the highest odds of achieving dryness, as well as ≥ 50% reduction from baseline UI episodes/day (type not specified). However, adverse events were not reported in this network meta-analysis.

Identification of DO in urodynamics does not appear to influence the outcome of onabotulinum toxin A injections in patients with UUI [269].

4.1.4.3.1.1 Summary of evidence and recommendations for bladder wall injection of botulinum toxin A

Summary of evidence	**LE**
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and improving QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy but discontinuation rates are high.	2a
There is a risk of increased PVR volume and UTI with onabotulinum toxin A injections.	2
The risk of bacteriuria after onabotulinum toxin A (100 U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A (100 U) is superior to anticholinergics and mirabegron for cure of UUI and improvement of symptoms of OAB at twelve weeks.	1a

Recommendations	**Strength rating**
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with OAB/UUI refractory to conservative therapy or drug treatment.	Strong
Warn patients of the limited duration of response, risk of UTI and possible prolonged need for clean intermittent self catheterisation prior to treatment with onabotulinum toxin A.	Strong

4.1.4.3.2 Sacral nerve stimulation

Sacral nerve stimulation involves placing electrodes adjacent to the sacral nerve roots and delivering an electric current to the area via an attached battery implanted in the buttock, which delivers low-amplitude stimulation resulting in modulation of neural activity and stabilisation of bladder electrical activity through a mechanism that is, as yet, not fully understood. In most centres, test stimulation with a temporary or permanent electrode is performed to assess response, before undertaking permanent stimulator implantation. Currently, the only

reliable predictor for treatment success in SNS is test stimulation. A SR did not find predictive factors of success due to low level of evidence of included studies (small, retrospective and heterogeneous populations) [270] .

All randomised studies suffer from the limitation that patients cannot be blinded to the treatment allocation since all recruited patients have to respond to a test phase before randomisation. A Cochrane review in March 2008 [271] identified three RCTs that investigated SNS in patients with refractory UUI. The majority of studies compared a strategy of immediate implantation with delayed implantation.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at six months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at six months compared with 1.6% of the control group [272]. The effect on QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions. The other RCT achieved similar results, although these patients had already been included in the first report [273].

The results of seventeen case series of patients with UUI, who were treated early with SNS, were reviewed [274]. After follow-up of one to three years, ~50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50–90% improvement, and 25% demonstrated < 50% improvement. Two case series describing the outcome of SNS, with a mean or median follow-up of ≥ 4 years [275, 276] reported continued success (> 50% improvement of original symptoms) in patients available for follow-up. Cure rates for UUI were 15% [276].

A more recent RCT comparing a strategy of onabotulinum toxin A injection (200 IU), repeated as required, against a strategy of test and, if indicated, subsequent permanent SNS, showed lower cure rates with SNS at six months: 20% in the onabotulinum toxin A group and 4% in the SNS group had complete resolution of UUI [277]. Forty-six per cent in the onabotulinum toxin A group and 26% in the SNS group had ≥ 75% reduction in the number of episodes of UUI [278]. Two-year follow-up data from 87% of participants in this trial suggest no significant differences in treatment outcomes over 2 years, although satisfaction rates and treatment endorsement remain higher with onabotulinum toxin. The rates of complete resolution of UI (5% for both) as well as ≥ 75% reduction in UUI episodes (22% onabotulinum toxin A vs. 21% SNS) were equivalent at the 2-year mark [279]. Sacral nerve stimulation revision and removal occurred in 3% and 9% of this cohort, respectively.

A 2018 review of studies including SNS with ≥ 6 months follow-up reported dry rates of 43–56% [280]. Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33–41% [276, 277]. In a sub-analysis of the RCT similar success rates were found in patients with or without urodynamic DO [281].

4.1.4.3.2.1 Summary of evidence and recommendation for sacral nerve stimulation

Summary of evidence	LE
Sacral nerve stimulation is more effective than continuation of failed conservative treatment for OAB/ UUI, but no sham controls have been used.	1b
Sacral nerve stimulation is similarly effective as onabotulinum toxin A 200 U injection at 24 months.	1b
In patients who have been implanted, 50% improvement of UUI is maintained in ≥ 50% of patients and 15% may remain cured at four years.	3
The use of tined, permanent, electrodes in a staged approach results in more patients receiving the final implant compared to those who have undergone temporary test stimulation.	4

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have overactive bladder/urge urinary incontinence refractory to anticholinergic therapy.	Strong

4.1.4.3.3 Laser treament

A recent SR evaluated the use of vaginal lasers in the treatment of OAB and evaluated short-term studies detailing minimal improvement [282]. In general the quality of reported studies were weak and long-term safety data were lacking. Before considering widespread use of laser for the treatment of SUI and OAB, additional good-quality studies with extended follow-up, systematic reporting of adverse events, and objective measures of outcomes (urodynamic, 24-hour pad test, voiding diaries) are required.

4.1.4.3.3.1 Summary of evidence and recommendation for laser treatment

Summary of evidence	LE
Vaginal laser therapy shows minimal OAB symptom improvement in the shortterm, with minimal complications, however, long-term efficacy and safety data are lacking.	3

Recommendation	Strength rating
Do not offer vaginal laser therapy to treat overactive bladder symptoms outside of a well regulated clinical research trial.	Strong

4.1.4.3.4 Cystoplasty/urinary diversion

4.1.4.3.4.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any segment can be utilised if it has the appropriate mesenteric length. Most of the evidence pertaining to cystoplasty comes from patients with neuropathic bladder dysfunction. One study did not find any difference between bivalving the bladder in the sagittal or coronal plane [283, 284]. The procedure can be done, with equal success by open or robotic techniques, although the latter takes more time [285].

There are no RCTs comparing bladder augmentation to other treatments for patients with OAB/UUI. Most often, bladder augmentation is used to correct neurogenic DO, small capacity or low-compliant bladders caused by fibrosis, chronic infection such as tuberculosis, radiation, or chronic inflammation from interstitial cystitis.

The largest case series of bladder augmentation in a mixed population of idiopathic and neurogenic UUI included 51 women [286]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. The results for idiopathic DO (58%) were less satisfactory than for neurogenic UUI (90%). Malignant transformation was not reported in this series; however, it has been documented in other series and a SR [287-289]. Fewer than 60 cases have been reported worldwide, and almost all are exclusively beyond 10 years after the original cystoplasty [290].

Adverse effects are common and have been summarised in a review with five to seventeen years follow-up of > 267 cases; 61 of which had non-neurogenic UUI [291]. Many patients may require CISC to obtain adequate bladder emptying (Table 2). It is unclear if mucolytic agents reduce mucus accumulation. The only RCT comparing various mucolytic agents did not find significant benefits with the use of N-acetylcysteine, aspirin, or ranitidine. In one small study (n = 40), subcutaneous octreotide immediately before, and for fifteen days after surgery yielded significant reductions in mucus production, the need for bladder irrigation to clear blockages, and mean duration of hospital stay [292]. Before cystoplasty, all potential complications should be outlined, and before and after surgery patients should be well supported by stoma/continence nurses.

Depending on the relative costs of onabotulinum toxin A and augmentation cystoplasty, the latter can be cost-effective within 5 years if the complication rate is low and duration of effect of onabotulinum toxin A is < 5 months [293].

Table 2: Complications of bladder augmentation

Short-term complications	Affected patients (%)
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4

Long-term complications	Affected patients (%)
CISC	38
UTI/bacteriuria	70% asymptomatic 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.1.4.3.4.2 Detrusor myectomy (bladder auto-augmentation)
Detrusor myectomy aims to increase bladder capacity and reduce storage pressure by incising or excising a portion of the detrusor muscle, to create a bladder mucosal bulge or pseudo-diverticulum. It was initially described as an alternative to bladder augmentation in children [294].

Two case series in adult patients with idiopathic and neurogenic bladder dysfunction demonstrated poor long-term results caused by fibrosis of the pseudo-diverticulum [295, 296]. This technique is rarely, if ever, used nowadays.

4.1.4.3.4.3 Urinary diversion
Urinary diversion remains a reconstructive option for patients with intractable UI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation. Patients may be offered irreversible urinary diversion surgery. Options include ileal conduit urinary diversion, orthotopic neobladder and heterotopic neobladder with Mitrofanoff continent catheterisable conduit. There is insufficient evidence to comment on which procedure leads to the most improved QoL.

A small study comparing ileal with colonic conduits concluded that there are no differences in the relative risks (RR) of UUT infection and uretero-intestinal stenosis. However, no studies that have specifically examined these techniques for treatment of intractable OAB/UUI [283]. Therefore, careful consideration of which operation is undertaken depends on thorough preoperative counselling, access to stoma/continence nurses, as well as patient factors to allow for fully informed patient choice.

4.1.4.3.4.4 Summary of evidence and recommendations for cystoplasty/urinary diversion

Summary of evidence	LE
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion specifically for treatment of idiopathic OAB.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term severe complications.	3
The need to perform CISC following augmentation cystoplasty is common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3
Detrusor myectomy is ineffective in adults with UUI.	3

Recommendations	Strength rating
Ensure patient counselling and lifelong support both prior to and after major surgery as a treatment for overactive bladder (OAB).	Strong
Offer augmentation cystoplasty to patients with OAB/UUI who have failed all other treatment options and have been warned about the possible small risk of malignancy.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of clean intermittent self-catheterisation (ensure they are willing and able to do so) and that they need life-long surveillance.	Strong
Do not offer detrusor myectomy as a treatment for UUI.	Weak
Only offer urinary diversion to patients who have failed less-invasive therapies for the treatment of OAB/UUI, who will accept a stoma and have been warned about the possible small risk of malignancy.	Weak

4.1.5 *Follow-up*

Follow-up for women with OAB is guided by the type of treatment instituted and local service capacity. Standardisation of follow-up pathways can therefore be difficult. Here, we provide recommendations based on best practice and standards from clinical trials.

4.1.5.1 *Recommendations for follow-up of patients with overactive bladder*

Recommendations	Strength rating
Offer early follow-up to women who have been commenced on anticholinergic or beta-3 agonist therapy.	Strong
Offer repeat injections of onabotulinum toxin A, as required, to women in whom it has been effective (refer to the manufacturer's guidance regarding the minimum timeframe for repeat injections).	Strong
Offer life-long surveillance to women who have a sacral nerve stimulation implant to monitor for lead displacement, malfunction and battery wear.	Strong
Offer cystoscopic surveillance to women with an augmentation cystoplasty due to the small risk of malignancy.	Weak

4.2 Stress urinary incontinence

4.2.1 *Epidemiology, aetiology, pathophysiology*

Stress urinary incontinence is defined as the involuntary loss of urine on effort or physical exertion, is a significant health problem worldwide with social and economic impact on women and society. It is estimated that the number of women in the USA with UI will have increased from 18.3 million in 2010 to 28.4 million in 2050 [297]. The prevalence of SUI appears to peak between 45 and 59 years of age [298].

Data regarding the association of UI with ethnicity are conflicting. In several studies, SUI is more common in white women than in women of African–American or Asian–American origin [299, 300]. Other factors positively associated with SUI include parity, obesity, previous hysterectomy or pelvic surgery, diabetes mellitus [301] and pulmonary disease [302]. Physical activity level is another important factor that is positively correlated with SUI severity [303].

Two common, often overlapping, mechanisms for SUI have been described: (1) urethral hypermobility resulting from loss of support of the bladder neck and urethra; and (2) weakness of the urinary sphincter itself (intrinsic sphincter deficiency), which can result from trauma, radiotherapy, previous pelvic or uro-gynaecological surgery, neurological disease or ageing.

The mechanism behind urethral hypermobility as a cause of SUI is based on the "vaginal hammock" hypothesis [304]. The endopelvic fascia, which is attached to the upper (abdominal) side of the PFMs, links the muscles to the vagina and represents the "hammock", which can compress the urethra during rest and activity. This compression, combined with intrinsic urethral sphincter pressure, supports and maintains the urethra in the correct and closed position, preventing involuntary loss of urine, despite any increases in intravesical pressure. Damage to the supporting tissues (particularly the arcus tendinous fasciae pelvis, the central part of the fascia) can result in urethral hypermobility. Consequently, rather than being compressed at times of increased intra-abdominal pressure, the urethra moves caudally, funnelling the bladder neck, and is no longer compressed, resulting in SUI [304, 305]. In general, almost all treatments are used for both subtypes of SUI, but in general most treatments are more successful in patients with some degree of urethral hypermobility than for isolated intrinsic weakness of the urinary sphincter [306].

4.2.2 *Classification*

Patients with SUI can be classified as uncomplicated and complicated [307]. The Panel has reached a consensus on the definition to be used throughout this guideline document:

- Women with uncomplicated SUI: no prior surgery for SUI, extensive pelvic surgery, or pelvic radiotherapy; no neurogenic LUT dysfunction; no bothersome genito-urinary prolapse; absence of voiding symptoms; and no medical conditions that affect the LUT. In cases where additional significant storage symptoms, especially OAB, are present, consider a possible diagnosis of MUI (see Section 4.3).
- Women with complicated SUI: previous surgery for incontinence or extensive pelvic surgery; history of pelvic irradiation; presence of anterior or apical POP; presence of voiding symptoms or neurogenic LUT dysfunction; and significant OAB/UUI. Neurogenic LUT dysfunction is reviewed in the EAU Guidelines on Neuro-Urology and will not be considered further in these guidelines [9]. The treatment of LUTS associated with genitourinary prolapse has been included in these guidelines (see Section 4.7).

4.2.3 ***Diagnostic evaluation***

4.2.3.1 *History and physical examination*

There is universal agreement that taking a history should be the first step in the assessment of anyone with UI. When the history categorises UI as probable SUI the presence of complicated or uncomplicated SUI can also be determined. Those patients who require rapid referral to an appropriate specialist can also often be identified from the clinical history.

There is little evidence from clinical trials that carrying out a clinical examination improves clinical outcomes, but there is widespread consensus that it remains an essential part of the assessment of women with SUI. It should include abdominal examination, vaginal examination and careful assessment of any associated POP, examination of the perineum and evaluation of PFM strength, as well as a neuro-urological examination. An attempt to reproduce the SUI should be made. A standing cough test has greater sensitivity for diagnosis of SUI compared with a supine cough test [308]. Despite this, the ICS has proposed a standardisation of the female cough stress test that includes a supine/lithotomy position with 200–400 mL fluid in the bladder and one to four coughs [309].

4.2.3.1.1 Summary of evidence and recommendation for history and physical examination

Summary of evidence	**LE**
A standing cough stress test is more sensitive than a supine test.	1b

Recommendation	**Strength rating**
Take a full clinical history and perform a thorough physical examination in all women presenting with stress urinary incontinence.	Strong

4.2.3.2 *Patient questionnaires*

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies did not include homogeneous populations of adult women diagnosed with SUI. This limits the extent to which results and conclusions from these studies can be specifically applied to women with SUI. Some questionnaires are used for prevalence studies; others are responsive to change and may be used to measure outcomes, although evidence on their sensitivity is inconsistent [26, 27]. There is no evidence to indicate whether use of QoL or condition-specific questionnaires has an impact on treatment outcome. To date, there is no one questionnaire that fulfils all requirements for the assessment of women with SUI.

4.2.3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	**LE**
Validated condition-specific symptom scores assist in the screening for and categorisation of UI.	3
Validated symptom scores measure the severity and troublesomeness of SUI.	3
Both condition-specific and general health status questionnaires measure current health status, and are responsive to change following treatment.	3

Recommendation	**Strength rating**
Use a validated and appropriate questionnaire as part of the standardised assessment of patients with stress urinary incontinence.	Strong

4.2.3.3 *Post-void residual volume*

It is important to evaluate PVR volume in patients with SUI; particularly in those who also have voiding symptoms or POP. The prevalence of a significant PVR volume in patients with SUI is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. Most studies investigating PVR volume have not included patients with SUI. In general, the data on PVR volume can only be applied with caution to adults with non-neurogenic SUI. In a cohort study of > 900 women with SUI, there was good correlation between PVR volume estimated by US and measured by catheterisation. The mean PVR volume was 39 mL measured by catheterisation and 63 mL estimated by US, with only 16% of women having PVR > 100 mL [59].

4.2.3.3.1 Summary of evidence and recommendations for post-void residual volume

Summary of evidence	LE
The majority of women with SUI do not have a significant PVR volume.	3
There is good correlation between PVR volume estimated using US and measured via catheterisation in women with SUI.	3

Recommendations	Strength rating
Measure post-void residual (PVR) volume, particularly when assessing patients with voiding symptoms or complicated stress urinary incontinence (SUI).	Strong
When measuring PVR volume, use ultrasound in preference to catheterisation.	Strong
Monitor PVR volume in patients scheduled for treatment that may cause or worsen voiding dysfunction, including surgery for stress urinary incontinence.	Strong

4.2.3.4 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, based on the assumption that it may help to provide or confirm diagnosis. The role of urodynamics in SUI evaluation remains poorly defined and is still under debate.

Invasive urodynamic tests are often performed prior to surgical treatment of SUI. Clinical diagnosis of incontinence and cystometric findings often do not correlate [67, 68]. The diagnostic accuracy of urethral pressure profilometry [69] and VLPP measurement in SUI is generally poor [310]. Measurement of MUCP correlates, albeit weakly, with incontinence severity [69], and there is conflicting evidence about its reproducibility [64, 65]. Methods of recording MUCP cannot be compared meaningfully [66]. Valsalva leak point pressures are not standardised and there is minimal evidence about reproducibility. Valsalva leak point pressure did not reliably assess incontinence severity in a cohort of women selected for surgical treatment of SUI [70]. The predictive value of the tests regarding treatment outcome remains unclear.

A Cochrane review including seven RCTs showed that urodynamic tests increased the likelihood of avoiding surgery for SUI. However, there is no evidence that this influence on decision-making alters the clinical outcome of treatment within trial populations [78].

A high-quality RCT (n = 630) compared office evaluation alone and combined with urodynamics in women with clinically demonstrable SUI about to undergo surgery. While urodynamics changed the clinical diagnosis in 56% of women [311], there was no difference in severity of SUI or any secondary outcome at twelve months' follow-up after SUI surgery [80]. A similar study also found that omission of urodynamics in the preoperative work-up of SUI did not lead to inferior results [312]. Patients in whom urodynamics were discordant with clinical assessment (n = 109) were randomly allocated to receive either immediate surgery or individually tailored therapy based on the urodynamic findings. In this trial, performing immediate surgery, irrespective of the result of urodynamics, did not result in inferior outcomes [313]. An RCT, in which 145 women were randomised to retropubic or trans-obturator MUS, concluded that when patients were stratified according to preoperative VLPP ($\leq$ or $>$ 60 cm H_2O), it was not linked to outcome after both synthetic MUS procedures [314].

Another study reported conflicting evidence. Valsalva leak point pressure or MUCP in the lowest quartile was predictive in terms of synthetic MUS failure at twelve months [83].

The Panel recognises that it may be valuable to use urodynamic test results to help select the optimum surgical procedure, but the evidence outlined above suggests that performing urodynamics in patients with uncomplicated SUI, which can be diagnosed based on detailed clinical history and demonstrated at examination, is not necessary. The role of urodynamics in complicated SUI is still under debate [315]. However, the Panel consensus is that urodynamics should be carefully considered in cases of SUI with associated storage symptoms; cases in which the type of incontinence is unclear; cases in which voiding dysfunction is suspected; and cases with associated POP or prior surgery for SUI. This is in line with other guideline documents in this area [67].

4.2.3.4.1 Summary of evidence and recommendations for urodynamics

Summary of evidence	LE
Preoperative urodynamic testing in women with uncomplicated, clinically demonstrable SUI does not improve surgical outcome for SUI.	1b
There is no consistent correlation between urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that preoperative DO is associated with surgical failure of MUS in women.	3

Recommendations	Strength rating
Do not routinely carry out urodynamic tests when offering treatment for uncomplicated stress urinary incontinence (SUI).	Strong
Perform preoperative urodynamic tests in cases of SUI with associated storage symptoms, cases in which the type of incontinence is unclear, cases in which voiding dysfunction is suspected, and cases with associated pelvic organ prolapse or prior surgery for SUI.	Weak
Perform urodynamic tests if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence as they are primarily tests of urethral function.	Strong

4.2.3.5 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of SUI, as well as a patient's response to treatment.

The clinical utility of pad tests for people with UI has been assessed in two SRs [92, 93]. A one-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g show good specificity but low sensitivity for diagnosis of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [94]. A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [95]. The usefulness of pad tests in quantifying severity and predicting treatment outcome is uncertain [92, 97]. Pad testing is responsive to change following successful treatment [98]. Pad testing using a standardised bladder volume (50% of cystometric capacity) has been suggested to allow for a more reliable assessment of UI in a small study of 25 women [99]. There is no evidence that one type of pad test is superior to another.

4.2.3.5.1 Summary of evidence and recommendations for pad testing

Summary of evidence	LE
A pad test can diagnose SUI accurately, but cannot determine the aetiology.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based pad testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on standardised pad tests can be used to measure treatment outcome.	2

Recommendations	Strength rating
Use a pad test of standardised duration and activity protocol.	Strong
Use a standardised pad test when quantification of stress urinary incontinence is required, especially to assess response to treatment.	Weak

4.2.3.6 Imaging

The role of imaging in SUI patients is limited. Many studies have evaluated imaging of bladder neck mobility by US and MRI, and concluded that SUI cannot be identified by a particular pattern of urethro-vesical movement [316]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with *de novo* SUI [317]. Studies have assessed the use of imaging to investigate the mechanism of action of

MUS inserted for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not mobility of the bladder neck [109]. Following MUS surgery, a wider gap between symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [110]. One study of 72 women post-synthetic suburethral MUS surgery has investigated the usefulness of translabial US to assess tape functionality. In this study different parameters were measured (distance from tape to urethra, position and shape during Valsalva manoeuvre, etc.) and concluded that tape position relative to the patient's urethra seems to play a role in treatment outcome [318]. The general role of US in the evaluation and follow-up of women with SUI is unclear, and further research is needed to establish its place in the clinical pathway.

Several imaging studies have investigated the relationship between sphincter volume and function [319] and sphincter volume and outcome of surgery [320] in women. However, no imaging test has been shown to predict the outcome of treatment for SUI. Imaging of the pelvic floor can identify levator ani detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of SUI.

4.2.3.6.1 Summary of evidence and recommendation for imaging

Summary of evidence	**LE**
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with UI.	2b

Recommendation	**Strength rating**
Do not carry out imaging of the upper or lower urinary tract as part of the routine assessment of stress urinary incontinence.	Strong

*4.2.4 **Disease management***

4.2.4.1 Conservative management

4.2.4.1.1 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for LUTS and SUI in many epidemiological studies [144, 145]. There is evidence that the prevalence of both UUI and SUI increases proportionately with body mass index (BMI) [321]. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population [145].

All the available evidence relates to women. Three SRs concluded that weight loss was beneficial in improving UI [143, 144, 322]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [323-327]. Two large studies in women with diabetes mellitus, for whom weight loss was the main lifestyle intervention, showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [323, 328]. There have been other cohort studies and case–control studies suggesting similar effects, including surgery for the morbidly obese [329-333].

In a prospective study in 160 consecutive women who underwent bariatric surgery, surgically induced weight loss was associated with a significant improvement in pelvic floor disorders, including UI [334]. Similar results reported by prospective single-centre studies investigating the effect of weight loss induced by bariatric surgery revealed that bariatric surgery was associated with substantially reduced UI at eleven months and three years [335, 336].

4.2.4.1.1.1 Summary of evidence and recommendation for obesity and weight loss

Summary of evidence	**LE**
Obesity is a risk factor for LUTS and UI in women.	3
Non-surgical weight loss improves UI in overweight and obese women.	1a
Surgical weight loss improves UI in obese women.	1b

Recommendation	**Strength rating**
Encourage overweight and obese women with LUTS/stress urinary incontinence to lose weight and maintain weight loss.	Strong

4.2.4.1.2 Urinary containment

The evidence for urinary containment derives from the same literature as for containment in OAB-wet. The readers are therefore referred to Section 4.1.4.1.3.

4.2.4.1.2.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	LE
Pads are effective in containing urine.	1b

Recommendations	Strength rating
Ensure that women with stress urinary incontinence (SUI) and their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of SUI, either for temporary symptom control or where other treatments are not planned.	Strong

4.2.4.1.3 Pelvic floor muscle training

Pelvic floor muscle training is used to improve function of the pelvic floor, thus improving urethral stability. An immediate effect of a single PFM contraction is narrowing of the levator hiatus area, increase of urethral closure pressure, and lifting of the bladder and rectum thus preventing occurrence of SUI [337-339]. In an RCT comparing intensive PFMT over a six-month period with no treatment, there were increased muscle strength and endurance, narrowing of the levator hiatus, reduced PFM length, increased muscle volume, and lifting of the bladder neck and rectal ampulla [340]. Pelvic floor muscle training may be used to prevent SUI; e.g., in childbearing women before birth, or as part of a planned recovery programme after childbirth. Most often, PFMT is used to treat existing SUI; sometimes in combination with observation and/or palpation of the muscle contraction by the therapist, or biofeedback (using an apparatus measuring the contraction either by electromyography, manometry, dynamometry, US or MRI). Electrical stimulation and vaginal cones are also used in treatment of SUI based on an assumption of the same mechanism of action.

4.2.4.1.3.1 Efficacy of pelvic floor muscle training

A Cochrane review compared PFMT with no treatment or inactive control treatment and found that women with SUI in the PFMT groups were eight times more likely to report cure (56% vs. 6%; four trials including 165 women; high-quality evidence) [341]. The review also documented significant improvement in SUI (seven trials, 376 women; moderate-quality evidence), and improvement in UI QoL (six trials, 348 women; low-quality evidence). Pelvic floor muscle training reduced leakage by one episode per day in women with SUI (seven trials, 432 women; moderate-quality evidence). Women with SUI in the PFMT groups lost significantly less urine in short (up to one-hour) pad tests. The comparison of short pad tests showed considerable heterogeneity but the findings still favoured PFMT when using a random-effects model (mean difference 9.71 g in four trials including 185 women; moderate-quality evidence). Women in the PFMT group were also more satisfied with treatment and their sexual outcomes were better. Adverse events were rare and minor.

A Cochrane review concluded that there may be some additional effect of adding biofeedback to PFMT. However, this was based on RCTs with training frequency and attention favouring biofeedback [342]. In a recent RCT (61.3% had MUI) comparing the exact same training dosage and attention between groups, use of biofeedback did not yield any additional effect [343]. Group training is cost-effective in treatment of SUI/UI compared to individual treatment [344]. Another Cochrane review concluded that combination of individual assessment/education and group training was equally effective compared to individual treatment, but again the dosage and attention differed between comparison groups [345]. In a more recent RCT with the exact same training dosage and attention in individual and group training, group training was not inferior to individual treatment [344]. It is worth noting that all of the PFMT interventions in these reviews follow individual assessment and teaching before starting PFMT, and most interventions use some sort of measurement tool (biofeedback) in the assessment.

Both the Cochrane review and the International Consultation on Incontinence (ICI) concluded that the use of vaginal cones to train the PFMs is more effective than no treatment, but it is inconclusive whether it is more or less effective than structured PFMT [341, 346, 347]. Some women are unable to maintain the cone inside, and some report discomfort and motivation problems and adherence may be low [346].

The Cochrane review [341], the ICI [347] and the National Institute for Health and Care Excellence (NICE) guidelines (2019) [67] all conclude that there is the highest level evidence (1a) to support PFMT in the treatment of SUI/MUI. All SRs conclude that PFMT is less effective if women with MUI and UUI are included in the studies and more effective with more intensive and supervised training. According to the NICE guidelines literature review, PFMT is as effective as surgery for around half of women with SUI, and due to the risks following surgery and absence of adverse effects of PFMT, they recommend three months of supervised PFMT as first-line treatment for SUI and MUI [67].

Pelvic floor muscle treatment was compared to synthetic MUS surgery in an RCT involving 460 women with moderate to severe SUI [348]. Crossover between treatment arms was allowed and 49.0% of women in the physiotherapy group and 11.2% of women in the surgery group crossed over to the alternative treatment. Subjective improvement was reported by 90.8% of women in the surgery group and 64.4% of women in the physiotherapy group at twelve months.

4.2.4.1.3.2 Efficacy of electrical stimulation

There is lack of consensus regarding the use of ES to treat SUI. For subjective cure of SUI, a Cochrane review found moderate-quality evidence that ES is probably better than no active treatment, risk ratio (RR): 2.31 [349]. Similar results were found for cure or improvement of SUI (RR: 1.73), but the quality of evidence was low. There is uncertainty as to whether there is a difference between ES and sham treatment in terms of subjective cure alone because of the very low quality of evidence (RR: 2.21). For subjective cure or improvement, ES may be better than sham treatment (RR: 2.03). Any comparison between ES and PFMT and other treatments is hampered by low-quality evidence. Adverse effects such as pain and discomfort have been reported, and ES is not tolerated by all women [349].

In an RCT, 132 women assessed by vaginal palpation to have 0–1 on the modified Oxford grading scale (unable to contract the PFM) were randomly assigned to an eight-week intervention of learning to contract via palpation, palpation with pelvic tilt, intravaginal ES, or verbal instruction [350]. The results showed that 63.6%, 69.7%, 33.3% and 18.2% in the four groups, respectively, scored two after the intervention. Palpation was significantly more effective that ES, but one third of the ES group had learned a correct PFM contraction [350]. The effect on UI measured by ICIQ-UI-SF was significantly better in the palpation group.

4.2.4.1.3.3 Long-term efficacy of pelvic floor muscle training

In a SR including nineteen studies, 1141 women were followed-up for one to fifteen years after PFMT for SUI [351]. Meta-analysis was not performed due to high heterogeneity of outcome measures and training dosage (frequency, intensity, duration and adherence). Only two studies provided interventions during follow-up. Losses to follow-up ranged between 0% and 39%. Long-term adherence to PFMT varied between 10% and 70%. Five studies reported that the initial success rate on SUI and MUI was maintained in the long term. Long-term success based on responders in the original trial varied between 41% and 85%. Surgery rates in the long term varied between 4.9% and 58%. It was concluded that short-term outcome of PFMT can be maintained at long-term follow-up without incentives for continued training, but there is a high heterogeneity in both interventional and methodological quality in short- and long-term PFMT studies [351].

4.2.4.1.3.4 Efficacy of pelvic floor muscle training in childbearing women

Pelvic floor muscle training to prevent SUI has been studied during pregnancy and in the postpartum period and the results are not reported separately for SUI and other subgroups of UI. A Cochrane review concluded that PFMT in women with and without UI (combined primary and secondary prevention) during pregnancy, produced a 26% reduced risk of UI during pregnancy and the mid-postnatal period [352]. Furthermore, pregnant continent women (primary prevention) who exercised the PFM during pregnancy were 62% less likely to experience UI in late pregnancy and had 29% lower risk of UI three to six months after giving birth. There is insufficient evidence for a long-term effect of antenatal PFMT beyond six to twelve months postpartum. Compared with usual care, there is no evidence that antenatal PFMT in incontinent women decreases incontinence in late pregnancy (very low-quality evidence), or in the mid- (low-quality evidence) or late postnatal periods (very low-quality evidence).

There have been fewer RCTs in the postpartum period than during pregnancy [352]. No primary prevention studies were found in women after birth. For PFMT started after delivery, in a mixed group of continent and incontinent women, there was uncertainty about the effect on UI risk in the late postnatal period (three trials, 826 women; moderate-quality evidence), and in postnatal women with persistent UI, there is no evidence that PFMT results in a difference in UI at more than six to twelve months postpartum (three trials; 696 women; low-quality evidence). However, another RCT found that UI was less frequent in the intervention group, with 57% of

patients still symptomatic, compared to 82% of controls, as was bladder-related problems with a prevalence of 27% in the intervention vs. 60% in the control group [353]. Randomised controlled trials of high interventional and methodological quality are needed in the postpartum period.

4.2.4.1.3.5 Pelvic floor muscle training in elderly women

There have been few RCTs on conservative treatment of SUI in elderly women (> 65 years) and many of the studies combined different modalities, such as bladder training, lifestyle modifications and PFMT [354]. Some of the studies on PFMT and SUI in the general population have included women > 65 years and PFMT seems to be equally effective in elderly women. A SR on conservative management included 23 trials, with nine of moderate-to-high methodological quality, and concluded that PFMT in combination with physical training was effective in reducing UI and improving QoL [355]. Prompted voiding and toileting assistance with functional exercise reduced UI. Other behavioural interventions such as night-time prompted voiding and waking routine had no effect on UI reduction. The most recent ICI consensus publication stated that although there are limited studies of PFMT on UI in frail elderly populations, age and frailty alone should not preclude the use of PFMT in appropriate patients with sufficient cognition to participate [354]. More high-quality RCTs, both in frail and healthy older women (> 80 years of age) are needed.

A SR from the Cochrane Database found insufficient evidence to state whether or not there were additional effects by adding PFMT to other active treatments (including vaginal cones, electromagnetic stimulation, biofeedback, continence pessary, drugs) when compared with the same active treatment alone for female SUI or mixed UI. However, these results should be interpreted with caution as most of the comparisons were investigated in small, single trials. Also, none of the included trials reported data on adverse events associated with the PFMT regimen, thereby making it very difficult to evaluate the safety of PFMT [356].

4.2.4.1.3.6 Summary of evidence and recommendations for pelvic floor muscle training

Summary of evidence	**LE**
Pelvic floor muscle training is better than no treatment for improving SUI and QoL in women with SUI and MUI across a range of outcomes, including cure rate, improvement rate, QoL, number and volume of urine leaks and treatment satisfaction.	1a
Pelvic floor muscle training exhibits a low rate of adverse events.	1a
Higher-intensity, supervised treatment regimens confer greater benefit in women receiving PFMT.	1a
There is no extra benefit of combining PFMT with biofeedback.	1b
Short-term benefits of intensive PFMT can be maintained in the long term.	2a
Pelvic floor muscle training in the antenatal period is associated with a reduced risk of UI in late pregnancy and in the short-term postnatally.	1a
Postpartum PFMT is effective in women with persistent UI.	1b
There is no benefit of postpartum PFMT in mixed (continent and incontinent) groups of women.	1b
Mid-urethral sling surgery is superior to PFMT for women with moderate-to-severe SUI.	1b
Pelvic floor muscle training commencing in the early postpartum period improves UI in women for up to 6 months.	1b
There is conflicting evidence on whether the addition of ES increases the effectiveness of PFMT alone.	2a

Recommendations	**Strength rating**
Offer supervised intensive pelvic floor muscle training (PFMT), lasting at least three months, as first-line therapy to all women with stress urinary incontinence (SUI) or mixed urinary incontinence (including elderly women and pre- and postnatal women).	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Balance the efficacy and lack of adverse events from PFMT against the expected effect and complications from invasive surgery for SUI.	Strong
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for treatment of SUI.	Strong

4.2.4.1.4 Electromagnetic stimulation

Electromagnetic stimulation (EMS) has been evaluated for its role in SUI therapy. In a double-blind RCT of EMS including 70 women with SUI, no effect of EMS over sham in any outcome was recorded [357].

4.2.4.1.5 Electroacupuncture

A SR including fifteen RCTs and women with SUI treated by electroacupuncture (EA) demonstrated that EA for SUI was effective (odds ratio [OR]: 5.64; 95% CI: 4.19-7.59; I^2: 22%). ICIQ-SF scores increased (SMD: -0.48; 95% CI: -0.62 to -0.33; I^2: 32%) and 1-hour urine leakage decreased (OR: -4.14; 95% CI: -4.69 to -3.33; I^2: 78%) in patients undergoing EA compared with those receiving sham EA, physical exercise or medication [358].

4.2.4.2 Pharmacological management

4.2.4.2.1 Oestrogen

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause.

Oestrogen treatment for SUI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [256-258]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

A Cochrane review looked at the use of oestrogen therapy in postmenopausal women given local oestrogen therapy and seventeen studies focused on SUI [256]. There is also a narrative review of oestrogen therapy in urogenital diseases [359]. The Cochrane review found that vaginal oestrogen treatment improved symptoms of SUI in the short-term [256]. There were small, low-quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, ES and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes, although more women preferred the ring device. In one trial, no significant adverse effects following vaginal administration of oestradiol for vulvovaginal atrophy over two years were reported [360].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. The ideal treatment duration and the long-term effects are uncertain. A review of local oestrogen treatment showed improvement of UI over placebo with vaginal rings, which were favoured subjectively over pessaries [361].

One RCT in postmenopausal women showed a benefit of adding intravaginal oestriol to vaginal ES and PFMT in female SUI [362].

Studies of systemic HRT with non-urogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo and no SUI improvement [363-368]. In a single RCT, use of raloxifene was not associated with development or worsening of UI [369]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [67, 370, 371].

4.2.4.2.1.1 Summary of evidence and recommendations for oestrogens

Summary of evidence	**LE**
Vaginal oestrogen therapy improves SUI for postmenopausal women in the short-term.	1a
Neoadjuvant or adjuvant use of local oestrogens is ineffective as an adjunct to surgery for SUI.	2b
Systemic HRT using conjugated equine oestrogens does not improve SUI and may worsen pre-existing UI.	1a

Recommendations	**Strength rating**
Offer vaginal oestrogen therapy to postmenopausal women with stress urinary incontinence (SUI) and symptoms of vulvo-vaginal atrophy.	Strong
In women taking oral conjugated equine oestrogen as hormone replacement therapy (HRT) who develop or experience worsening SUI, discuss alternative HRT.	Strong

4.2.4.2.2 Duloxetine

Duloxetine inhibits the presynaptic reuptake of neurotransmitters, serotonin (5-hydroxytryptamine; 5-HT) and

noradrenaline (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurons, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

Duloxetine was evaluated as a treatment for female SUI or MUI in three SRs [170, 372, 373]. Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in the Urinary Incontinence QoL questionnaire was not found in the study, which used this as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [374], duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment in this trial.

Two open-label studies with a follow-up of ≥ 1 year evaluated the long-term effect of duloxetine in controlling SUI [375, 376]. Both studies had a high patient withdrawal rate, due to lack of efficacy and a high incidence of adverse events, including nausea and vomiting (≥ 40% of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue.

A SR showed significant efficacy for duloxetine compared to placebo in women with SUI, but with increased risk of adverse events [373]. The adverse effects of duloxetine include mental health problems and suicidal ideation. A meta-analysis of four RCTs including 1910 women with SUI reported no suicidality, violence or akathisia events, but suggested that discontinuation rate due to adverse events was around one in seven and that the harm may outweigh the benefit of treatment [377]. A meta-analysis of twelve placebo-controlled trials involving almost 3000 patients showed that, in patients with major depressive disorders, there were no significant differences in the incidence of suicide-related events with duloxetine vs. placebo [378].

4.2.4.2.2.1 Summary of evidence and recommendations for duloxetine

Summary of evidence	**LE**
Duloxetine improves SUI in women, but the chances of cure are low.	1a
Duloxetine may cause significant gastrointestinal and central nervous system adverse effects, leading to a high rate of treatment discontinuation, although these symptoms may be limited to the first weeks of treatment.	1a

Recommendations	**Strength rating**
Offer duloxetine (where licensed) to selected patients with stress urinary incontinence unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Strong
Duloxetine should be initiated and withdrawn using dose titration because of the high risk of adverse events.	Strong

4.2.4.2.3 Adrenergic agonists

A SR from the Cochrane Database including 22 RCT involving 673 women and seven different adrenergic drugs (phenylpropanolamine in eleven trials, midodrine in two, norepinephrine in three, clenbuterol in another three, terbutaline in one, eskornade in one and Ro 115-1240 in one) found weak evidence that adrenergic agonists may improve SUI. Moreover, side effects did occur but were usually minor. More evidence is needed to compare adrenergic drugs with other drugs for SUI and also with PFMT [379].

4.2.4.3 Surgical management

4.2.4.3.1 General considerations

The use of polypropylene mesh as synthetic MUS for the treatment of SUI has recently come under scrutiny following concerns about long-term complications. In some European countries such as the UK, the use of synthetic MUS has been paused and pelvic mesh was the subject of a parliamentary review published in July 2020 [380]. This review concluded that *"For many women mesh surgery is troublefree and leads to improvements in their condition. However, this is not the case for all. There is no reliable information on the true number of women who have suffered complications. While they may be in the minority, that does not diminish the catastrophic nature of their suffering or the importance of providing support to them and learning from what has happened to them".*

The range of complications highlighted during the process of this parliamentary review included [380]:

- pain;
- recurrent infections;
- mobility issues;
- recurring or new incontinence/urinary frequency;
- recurring or new prolapse;
- haemorrhage;
- bowel issues;
- erosion of mesh; this can be into the vagina and/or other organs;
- sexual difficulties; including pain on intercourse and a loss of sex life;
- autoimmune issues;
- psychological impacts.

When considering the choice of surgical treatments for SUI the Panel advises individual clinicians to abide by any national or local rules that may be in place regarding mesh surgery. It is essential for clinicians to point out the deficiencies in the long-term evidence regarding mesh use in SUI with specific reference to the complications highlighted above.

In line with the recommendations from NICE [67] and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) paper [381], the Panel agrees that surgeons and centres performing surgery should:

- be trained in the field of incontinence and for each surgical procedure they perform/offer;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for long-term follow-up.

The establishment of accurate and complete databases registering the interventions, patient profiles and surgical complications or all surgical treatments for SUI is recommended to allow the generation of robust long-term data.

Many surgical procedures are available for uncomplicated SUI patients and the Panel analysed the results of the different procedures in terms of clinical effectiveness, safety and cost-effectiveness based on the recent ESTER SR and economic evaluation [382] and previous SRs including those from the Cochrane Collaboration [383-387].

The outcome parameters used to evaluate surgery for SUI have been limited to:

- continence rate;
- patient-reported outcome measures;
- general and procedure-specific complications;
- generic, specific (UI) and associated (sexual and bowel) QoL.

In this context, it has to be taken into account that a number of products may no longer be available and therefore the recommendations may not be transferable to current devices. The Panel makes a strong recommendation that new devices are only used as part of a structured research programme and their outcomes monitored in a registry, until there is adequate evidence of safety and efficacy.

4.2.4.3.1.1 Recommendations for surgical treatment

Recommendations	Strength rating
Offer patients who have explored/failed conservative treatment options a choice of different surgical procedures, where appropriate, and discuss the advantages and disadvantages of each approach.	Strong
Use new devices for the treatment of stress urinary incontinence only as part of a structured research programme. Their outcomes must be monitored in a registry or as part of a well-regulated research trial.	Strong

4.2.4.3.1.2 Shared decision making

The Panel recognises that a shared decision-making approach is paramount when any treatments are proposed but felt particular emphasis should be made for the topic area of surgical treatment for incontinence.

There are a number of different options available for patients which vary in both efficacy and safety profile. Consequently, the amount of information given to patients considering surgery for SUI is substantial. The Panel would unequivocally advise adherence to the fundamental principles of the shared decision-making process which include:

- full participation from the patient;
- delivery of factual information regarding benefits and risks of any particular treatment, if possible adapted to the specific situation of the patient;
- delivery of information about the experience and expertise of the HCP/institution delivering the treatment, especially for highly-specialised procedures such as complex SUI and mesh removal surgery;
- confirmation that the patient understands the information given;
- clinician understanding and documenting individual patient preferences;
- facilitation of deliberation and initial decision-making;
- patient opportunity to consider and confirm any decisions made;
- clinician assistance with implementation of the final decision.

4.2.4.3.2 Surgery for women with uncomplicated stress urinary incontinence

The principal procedures evaluated are:

- open and laparoscopic colposuspension;
- autologous “traditional” slings;
- bulking agents;
- synthetic MUS.

4.2.4.3.2.1 Open- and laparoscopic colposuspension surgery

Open colposuspension was previously considered the most appropriate surgical intervention for SUI, and was used as the comparator in RCTs of newer, less-invasive surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

Open colposuspension

A number of SRs have covered open surgery for SUI, with a large number of RCTs [382, 384-387]. The Cochrane review on open colposuspension [387] included 55 trials comprising 5417 women. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Within the first year, complete continence rates of 85–90% were achieved for open colposuspension, while failure rates in terms of recurrent UI were 17% up to five years and 21% at > 5 years. The risk of reoperation after Burch colposuspension is estimated at 6% within five years [78] and 10.8% within nine years [388]. The reoperation rate specifically for UI was only 2%. Colposuspension was associated with a higher rate of development of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) at five years compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocoele was similar after colposuspension (37%) and after TVT (41%). The Cochrane review concluded that open colposuspension is an effective treatment for SUI and around 70% of women can expect to be dry at five years after surgery.

Laparoscopic colposuspension

A Cochrane review reported on twelve trials comparing laparoscopic to open colposuspension [385]. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were poorer for laparoscopic colposuspension. The ESTER SR [382] showed, based on a network meta-analysis, that at twelve months open colposuspension was more effective than laparoscopic colposuspension (nine trials) but these findings were based on low-quality evidence. The Surface Under the Cumulative Ranking (SUCRA) score, which is a numerical representation of the overall ranking and presents a single number associated with each intervention, was 76.7% after open colposuspension and 48.9% after laparoscopic colposuspension. Laparoscopic colposuspension had a shorter duration and subsequent hospital stay and may be slightly more cost-effective when compared with open colposuspension after 24 months’ follow-up. Single-port laparoscopic Burch can be an alternative treatment, although data confirming efficacy are limited [389].

Complications

Voiding difficulties are more common after laparoscopic colposuspension than after retropubic MUS (7.5% vs. 5.1%) [382]. There was no difference between open colposuspension and retropubic MUS (7.8% vs 7.5%; OR: 0.87) [382]. The results for the comparisons of *de novo* symptoms of urgency or UUI between open colposuspension and retropubic MUS (11% vs. 8%; OR: 1.49) did not favour either treatment and showed wide confidence intervals [382]. The rate of bladder or urethral perforation was higher for laparoscopic colposuspension compared with open colposuspension (3.7% vs. 0.7%; OR: 4.65) [382].

4.2.4.3.2.1.1 Summary of evidence and recommendation for open and laparoscopic colposuspension surgery

Summary of evidence	LE
High subjective cure rates are associated with both open and laparoscopic colposuspension for treatment of SUI.	1a
Objective cure rates are higher for open compared to laparoscopic colposuspension.	1a
Colposuspension is associated with a higher long-term risk of POP than MUS.	1a
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a
Laparoscopic colposuspension is associated with higher rates of intraoperative bladder perforation and postoperative voiding dysfunction compared to open colposuspension.	1a
The rates of *de novo* urinary urgency following colposuspension are similar to other surgical treatments for SUI.	1a

Recommendation	Strength rating
Offer colposuspension (open or laparoscopic) to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.2 Autologous sling

In the past, autologous, cadaveric, xenograft, and synthetic materials have been used for bladder neck pubovaginal sling. Nowadays, use of autologous tissue, either rectus sheath or fascia lata, is the most studied material with the strongest evidence base to support its use [390]. The ESTER SR included three trials of autologous sling vs. open colposuspension, six trials of autologous sling vs. retropubic MUS and one trial of autologous sling vs. transobturator MUS. The quality of evidence was overall very low. The pooled estimate showed that fascial sling had a higher cure rate at one year than open colposuspension (OR: 1.24), retropubic MUS (OR: 1.06) and transobturator MUS (OR: 1.44) but without significance. The SUCRA score was 89.4% for women cured after autologous fascial sling. A sub-analysis from a Cochrane review showed autologous slings had better effectiveness compared to colposuspension at one to five years' follow-up [387]. In an RCT of Burch colposuspension vs. autologous slings, complete continence rates decreased substantially over time in both arms. At five years, the continence rate of colposuspension was 24.1% compared to 30.8% for fascial slings. Satisfaction remained higher in the sling group (83% vs. 73%) and was directly related to continence status [391].

Complications

Adverse events rates were similar for the two treatment groups (Burch 10% and sling 9%) although postoperative obstruction was found exclusively in the sling group. Voiding difficulties appear to be more common after autologous sling (15.4% vs. 10.2%; OR: 1.46) than after retropubic MUS. Compared with open colposuspension, the rate of bladder or urethral perforation was lower for traditional sling (0.6% vs. 3.0%; OR: 0.20) [382].

4.2.4.3.2.2.1 Summary of evidence and recommendation for autologous sling

Summary of evidence	LE
High cure rates are associated with autologous sling placement for treatment of SUI.	1a
Autologous sling is more effective in terms of cure rate than colposuspension.	1a
Autologous sling has a similar rate of adverse events compared to open colposuspension, with higher rates of voiding dysfunction and postoperative UTI, but lower rates of POP and bladder or urethral perforation.	1a

Recommendation	Strength rating
Offer autologous sling placement to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.3 Urethral bulking agents

The concept of this procedure originates from the idea that intra- or periurethral injection of an agent able to form artificial cushions under/around the urethra increases resistance at the bladder outlet and facilitates continence.

Two Cochrane reviews (2012 and updated in 2017) identified fourteen RCTs or quasi-RCTs of treatment for UI in which at least one management arm involved peri- or transurethral injection [392, 393]. Five additional reviews investigated the effect of injectables for the treatment of female SUI [394-398] independently of the injected material. One review included results from RCTs only [398]. In the most recent Cochrane review, 1814 patients were included from fourteen trials of seven different types of intraurethral injection: glutaraldehyde cross-linked collagen (Contigent©), a porcine dermal implant (Permacol©), solid silicone elastomer (Macroplastique©), autologous fat, pyrolytic carbon (Durasphere©), calcium hydroxylapatite (Coaptite©), hydrogel (Bulkamid®) and dextran polymer (Zuidex©). The conclusions state that the available evidence base remains insufficient to guide practice [393].

A SR of 23 studies using Macroplastique© including 958 patients showed a 75% improvement with 43% dry rate at < 6 months and a 64% improvement and 36% cure rate at > 18 months [395]. A review of 514 elderly women with SUI treated with various agents showed a reduced pad weight in 73% at one-year follow-up, independent of the material injected [399]. The heterogeneity of the populations, the variety of materials used and the lack of long-term follow-up limit guidance for practice. Most of the studies showed a tendency for short-term improvement in UI, with the exception of one RCT, which did not find a difference between saline and fat injection [400].

One trial of 30 women showed a weak, non-significant advantage in terms of patient satisfaction after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels [393]. Two trials found a higher risk of urinary retention with intraurethral injections compared with transurethral injections, although the latter were associated with a higher risk of temporary urinary retention [392, 401]. A small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [402]. One study treated patients who had received radiotherapy with injection of Bulkamid® and reported ~25% cure at short-term follow-up [403].

Bulking agent injection is generally safe and the most frequent adverse event is UTI. However, autologous fat or hyaluronic acid should not be used due to the risk of fatal embolism and local abscess formation, respectively [392, 400].

Comparison with other surgical procedures

Two RCTs compared collagen injection to conventional surgery for SUI (silicon particles vs. autologous sling and collagen vs. other surgical procedures). The studies reported greater efficacy but higher complication rates for open surgery [404, 405].

In a recent non-inferiority clinical trial, women with primary SUI were randomised to TVT or polyacrylamide hydrogel urethral bulking agent injection (Bulkamid®) [406]. Mid-urethral TVT slings were associated with better satisfaction and cure rates than Bulkamid® in primary SUI. For objective cure rate, the cough stress test was negative in 95.0% of patients who underwent TVT vs. 66.4% who underwent Bulkamid®.

Another SR examining the relative efficacy of urethral bulking agents [407] included six studies in the quantitative synthesis for a total of 710 patients. The authors found that bulking agents are less effective than other surgical procedures according to subjective improvement after treatment (Relative risk [RR]: 0.70; 95% CI: 0.53-0.92, p = 0.01). However, the main limitation of this SR and meta-analysis was the absence of a common objective outcome measure to evaluate effectiveness.

4.2.4.3.2.3.1 Summary of evidence and recommendations for urethral bulking agents

Summary of evidence	**LE**
Urethral bulking agents may provide short-term improvement and cure in women with SUI.	1b
Bulking agents are less effective than MUS, colposuspension or autologous sling for cure of SUI and repeat injections may be required in order to achieve sustained benefits.	1b
Autologous fat and hyaluronic acid as bulking agents have a higher risk of adverse events.	1a
Adverse event rates for urethral bulking agents are lower compared to open surgery.	2a

There is no evidence that one type of bulking agent is better than another.	1b
The periurethral route of injection of bulking agents may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations	Strength rating
Offer urethral bulking agents to women seeking surgical treatment for stress urinary incontinence (SUI) following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Offer urethral bulking agents to women with SUI who request a low-risk procedure with the understanding that efficacy is lower than other surgical procedures, repeat injections are likely, and long-term durability and safety are not established.	Strong
Do not offer autologous fat and hyaluronic acid as urethral bulking agents due to the higher risk of adverse events.	Strong

4.2.4.3.2.4 Laser treatment

A SR including sixteen published studies, involving 899 patients with SUI, evaluated effects of laser treatment. The change in the ICIQ-SF score at one, two and sixth months was -5.49 (95% CI: -6.74 to -4.24; I^2: 91%; p<0.01), -4.97 (95% CI: -6.24 to -3.71), and -5.48 (95% CI: -6.15 to -4.81), respectively. The improvement in an one-hour pad weight test results at one, three and twelve months post treatment was -5.59 (95% CI: -6.93 to -4.25), -4.96 (95% CI: -6.73 to -3.20), and -5.82 (95% CI: -6.77 to -4.87), respectively. The PISQ-12 score increased by 5.39 (95% CI: 1.20-9.58) following treatment. Subgroup analysis identified the type and severity of UI as the potential source of heterogeneity. Adverse effects were reported in sixth of the sixteenth trials and affected only a small number of patients. Most adverse events were mild or moderate and required no medical intervention or resolved in a few days. According to this SR, vaginal laser therapy appears to be a safe, effective, and minimally invasive treatment option for SUI that can be well tolerated by patients [408].

Another SR including a total of 27 studies, evaluated the effects of Er:YAG and Fractional CO_2 lasers. The overall quality of studies was poor, and 23/27 studies were case series (LE:4). Er:YAGlaser showed a modest reduction in mild SUI cases, with benefits lasting a maximum of thirteen to sixteen months. Fractional CO_2 laser showed an improvement of mild SUI in few studies; however, no long-term data are available. When reported, adverse events were insignificant, however, they were not reported systematically [282].

Overall, SR have been noted in the current literature regarding vaginal lasers, including variation in laser settings and protocols, short-term follow-up, lack of urodynamic evaluation, and poor reporting of appropriate objective measures and adverse events. Based on the available literature, lasers cannot currently be recommended as a treatment option for SUI.

4.2.4.3.2.4.1 Summary of evidence and recommendations for laser treatment

Summary of evidence	LE
Several limitations have been noted in the current literature regarding vaginal laser treatment for SUI. These include variation in laser settings and protocols, short-term follow-up, lack of urodynamic evaluation, and poor reporting of appropriate objective measures and adverse events.	1b

Recommendations	Strength rating
Do not offer vaginal laser therapy to treat stress urinary incontinence symptoms outside of a well regulated clinical research trial.	Strong

4.2.4.3.2.5 Mid-urethral slings

Early clinical studies identified that non-autologous synthetic slings should be made from monofilament, nonabsorbable material, typically polypropylene, constructed as a 1–2 cm-wide mesh with a large pore size (macroporous) and coloured to facilitate removal [409]. Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

Transobturator route versus retropubic route

A Cochrane meta-analysis of MUS procedures for SUI in women was performed in 2017, spanning January 1947 to June 2014 [410]. Moderate-quality evidence from 55 studies showed variable, but comparable,

subjective cure rates between retropubic (71–97%) and transobturator (62–98%) slings in the short term (up to one year). No difference in the objective cure rate in the short term was found. However, the ESTER SR [382], based on a network meta-analysis including 36 trials of overall moderate quality, showed that at twelve months retropubic MUS was more effective than transobturator MUS (OR: 0.74). The SUCRA scores for women cured after retropubic MUS were 89.1% vs. 64.1% after transobturator MUS. However, there was no significant difference in these cure rates between the two approaches. Similarly, based on 40 moderate-quality trials, retropubic MUS performed better than the transobturator approach in terms of symptom improvement (RR: 0.76) but the difference was again not significant.

Analysis of a randomised equivalence trial of retropubic vs. transobturator MUS for the treatment of SUI in women shows similar findings. This trial confirms equivalence of objective cure rates at twelve but not at 24 months (77.3% and 72.3% objective cure rate for retropubic and transobturator surgery). For both types of MUS, subjective and objective treatment success decreased over time and equivalence of the retropubic and the transobturator routes could not be confirmed at 24 and 60 months, with retropubic MUS demonstrating an increased benefit, despite satisfaction remaining high in both arms [411]. Five years after surgical treatment, objective success was 7.9% greater in women assigned to retropubic sling compared to transobturator sling (51.3% vs. 43.4%), not meeting prespecified criteria for equivalence. Patient satisfaction decreased over five years but remained high and similar between treatment arms (retropubic sling 79% vs. transobturator sling 85%) [412].

In terms of long-term complications, data are scant but in one study *de novo* OAB developed in 14% of patients at ten years, with no significant differences between groups (TOT vs. TVT) [413]. In a multicentre prospective study of women undergoing TOT, failure of previous anti-incontinence procedures was the only predictor of recurrence of SUI [413].

A long-term cohort study of retropubic TVT showed an 89.9% objective cure rate and a 76.1% subjective cure rate at ten years. Overall, 82.6% of patients reported high satisfaction with surgery [414]. A long-term prospective study on transobturator sling showed that, at 145 months, the objective and subjective cure rates were 78.9% and 62.6% respectively; with no significant deterioration in SUI cure rates over time [415]. Another long-term follow-up study of patients treated with TVT showed a sustained response with 95.3%, 97.6%, 97.0% and 87.2% of patients being cured or improved at five, seven, eleven and seventeen years, respectively [416]. The ESTER network meta-analysis based on cure and improvement suggested that, when comparing surgical treatments for SUI, retropubic MUS, transobturator MUS and traditional sling had the highest efficacy, but this ranking does not consider the complication profile of these techniques. The short- to medium-term adverse event data are sparse [382]. The nine procedures compared in ESTER with their associated SUCRA ratings are shown in Table 3.

Table 3: SUCRA curve values for the outcome - number of women cured (indicated by %)

Procedure*	SUCRA rating
Traditional sling operations	89.4%
Retropubic MUS operations	89.1%
Open colposuspension	76.7%
Transobturator MUS operations	64.1%
Laparoscopic colposuspension	48.9%
Single-incision sling operations	39.8%
Bladder neck needle suspension	26.9%
Anterior vaginal repair	12.5%
Pelvic floor muscle training	2.6%

**Adapted from ESTER [363].*

Several health economic analyses of MUS procedures have been published with conflicting results. In a review of 26 economic evaluations and on the basis of a cost–utility and value of information analysis over a ten-year period, the authors concluded that MUS remains among the most cost-effective approaches [383]. A primary economic evaluation of retropubic vs. transobturator tapes over a five-year time period suggested that the latter may be cost-effective and cost-saving compared to the standard TVT approach [417]. Conversely, the findings from the ESTER network meta-analysis stated that over a lifetime, retropubic MUS was, on average, the least costly and most effective surgery but the level of uncertainty in these analyses was high.

Insertion using a skin-to-vagina direction versus a vagina-to-skin direction

The Cochrane review on MUS for female SUI showed no difference in the short- and medium-term subjective cure rates in vagina-to-skin (inside-out) vs. skin-to-vagina (outside-in) approaches, based on moderate-quality evidence [418]. Voiding dysfunction seems to be more frequent in the vagina-to-skin (inside-out) TOT group but this approach is associated with a lower frequency of vaginal perforations (RR: 0.25). Due to the low quality of the evidence, it is unclear whether the lower frequency of vaginal perforations with this approach is responsible for the lower rate of vaginal tape erosions. Likewise, a meta-analysis of RCTs demonstrated no significant difference in efficacy between outside-in and inside-out approaches, but vaginal perforations were, again, less frequent in the latter group (2.6% vs. 11.8%, OR: 0.21) [419]. The five-year data of a prospective, non-RCT of the two techniques showed a high objective success rate (82.6 vs. 82.5%, respectively) with no difference between the two approaches [420]. In a secondary analysis of the E-TOT study (a study of transobturator MUS in the treatment of women with urodynamic MUI), no difference in the patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to-vagina (outside-in) groups (63.2% and 65.5%, respectively; OR: 1.11) at nine years' follow-up [421].

Complications of synthetic mid-urethral slings

The ESTER network meta-analysis noted that comparative assessment of adverse events between different procedures was not always possible due to the lack of available data [382]. Direct comparisons using head-to-head meta-analyses were mainly carried out for retropubic MUS, transobturator MUS or single-incision slings. The authors did, however, comment that "For other intervention comparisons, the number of studies was generally small and the CIs wide. However, there was some evidence to suggest that bladder perforation was more likely to occur after retropubic MUS than after transobturator MUS, open colposuspension or traditional sling". In particular, the retropubic approach for MUS was associated with a significantly higher rate of bladder perforation than transobturator MUS was (5% vs. 0.2%). Regarding voiding dysfunction, 36 studies compared transobturator MUS with retropubic MUS, favouring the former (OR: 0.51). For pain, it is worth noting that it was defined and measured in many different ways across individual trials and across Cochrane reviews. Some pain outcomes were categorised by location (e.g., suprapubic) or time (e.g., short or long term). These discrepancies made it difficult to combine data from different studies. Data were available mainly for the comparison between retropubic and transobturator MUS and other surgical procedures. However, groin pain was more frequent after transobturator MUS than retropubic MUS (6.3% vs. 1.3%; OR: 3.80). Converse findings were reported for suprapubic pain, which was higher following TVT (1.2% vs. 4.0%; OR: 0.37). Visceral injury (0.5% vs. 2.4% OR: 0.36), mean operating time, intraoperative blood loss and hospital stay were lower in the transobturator than retropubic MUS groups. The overall vaginal erosion risk was low and comparable in both groups [382].

The rate of tape/mesh exposure or extrusion between retropubic and transobturator MUS was similar (2.1% vs. 2.4%; OR: 1.10). The exact time points at which measurements occurred could not be derived from the Cochrane reviews but most studies were reported to have a short follow-up period (≤ 12 months), with only a few studies having ≥ 2 years' follow-up [382]. Repeat surgery for UI was more common in the transobturator group (RR = 8.79); however, the data are limited and of low quality.

A population-based study performed in Scotland in > 16,000 women with SUI showed a similar rate of complications between mesh and non-mesh surgery [422]. However, a recent study of > 92,000 patients followed in the UK National Health Service showed a significant (9.8%) rate of complications using a more broad definition, and following patients for a longer period [423]. The level of detail regarding the precise nature of complications in this paper was poor. These findings suggest that, as with any SUI surgery, MUS can be associated with complications and fully informed consent is mandatory.

In general, the available published evidence would suggest that MUS does not seem to be associated with significantly higher rates of morbidity and complications compared to other surgeries for SUI, such as open retropubic colposuspension. Pelvic organ prolapse is more common after colposuspension while voiding dysfunction occurs more often after MUS [387]. The ESTER review has commented that the level of detail regarding short-to-medium adverse event data is poor for all SUI surgeries [382] and the Panel is aware of the recent findings from the Independent Medicines and Medical Devices Safety Review in the UK that has raised the possibility that the level of complications from synthetic MUS may be higher than the medical literature would suggest [380].

The ESTER SR included seven studies comparing reintervention after transobturator and retropubic MUS [382]. Pooled analysis of these studies showed wide CIs and considerable uncertainty around the estimated OR (twelve-month post-surgery: 1.37). At one to five years after the procedure, rates of repeat continence

surgery were higher in women undergoing transobturator MUS (18.3%) compared with retropubic MUS (0.5%), although only two studies were available for the analysis. A similar trend was observed in studies with a longer follow-up period (> 5 years) but the pooled analysis of these studies showed wide CIs. For retropubic MUS surgery, the bottom-to-top route was 10% more efficacious than top-to-bottom in terms of subjective cure and it was associated with less voiding dysfunction, bladder perforations and vaginal erosion [382].

Single-incision mid-urethral slings
Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operation. It should also be noted that some devices have been withdrawn from the market (e.g., TVT Secur®, Minitape, MiniArc®), and yet evidence relating to these devices may still be included in current meta-analyses. There is evidence to suggest that single-incision slings are quicker to perform and cause less postoperative thigh pain, but there is no difference in the rate of chronic pain. There is insufficient evidence for direct comparisons between single-incision slings, and no conclusions have been reached about differences between devices.

The ESTER SR showed, based on low-quality evidence, that at twelve months, retropubic and transobturator MUS were more effective than single-incision sling (TVT, OR: 0.50; TOT, OR: 0.68). The SUCRA score was 39.8% for women cured after single-incision slings. However, since not all single-incision devices have been assessed in a comparative RCT, it may be unsafe to assume that they are collectively technically similar or exhibit the same levels of efficacy.

Little data exists regarding the systematic reports of sling complications. When existing, the main limitations are heterogeneity of cohorts, poor long-term follow-up, and lack of evidence on the effective management of mesh-related complications [424]. A prospective registry will be required to generate meaningful outcome data and help in the complex management of patients who have mesh-related complications.

Complications of single-incision slings
Meta-analysis of comparison between single-incision sling and transobturator MUS showed similar rates of mesh erosion or extrusion between interventions (4.8% vs. 3.7%; OR: 1.23). Rates of postoperative pain were higher after retropubic MUS than after single-incision slings (19.2% vs. 6.8%; OR: 0.21).

The rate of unspecified pain was higher after transobturator MUS than after single-incision sling at twelve months (1.0% vs. 5.2%; OR: 0.24) and 24 months (1.4% vs. 10.4%; OR: 0.16). Single-incision sling was associated with more repeat surgery compared with transobturator MUS (5.1% vs. 2.9%; OR: 1.57). At > 3 years after the procedure, the repeat surgery rate was 10.3% for single-incision slings vs. 7.6% for transobturator MUS (OR: 1.42) [382].

Sexual function after synthetic mid-urethral sling surgery
A SR examining the effect of synthetic MUS on female sexual function suggested different and contradictory results between studies. More studies have shown an improvement, or no change, in sexual function because of a reduction in coital incontinence, anxiety and avoidance of sex. Dyspareunia was the most common cause of worsening of sexual function and the precise incidence is difficult to estimate as many studies did not report it [425]. A meta-analysis of outcome measures in trials of sling procedures suggests that single-incision slings are associated with a significantly higher improvement in sexual function compared to standard MUS procedures [426].

4.2.4.3.2.5.1 Summary of evidence and recommendations for mid-urethral slings

Summary of evidence	**LE**
The retropubic MUS appears to provide better patient-reported subjective and objective cure of SUI, compared with colposuspension.	1a
Synthetic MUSs inserted by the transobturator or retropubic route provide equivalent patient-reported outcomes at 1 year.	1a
Synthetic MUSs inserted by the retropubic route have higher patient-reported cure rates in the longer term.	1b
Long-term analyses of MUS cohorts showed a sustained response beyond 10 years.	2b
The retropubic route of insertion, compared with the transobturator route, is associated with a higher intraoperative risk of bladder perforation and a higher rate of voiding dysfunction.	1a
The transobturator route of insertion is associated with a higher risk of groin pain than the retropubic route.	1a

Long-term analysis of MUS showed no difference in terms of efficacy for the skin-to-vagina (outside-in) compared to vagina-to-skin (inside-out) directions up to 9 years.	2a
The top-to-bottom (inside-out) direction in the retropubic approach is associated with a higher risk of postoperative voiding dysfunction.	1b
The comparative efficacy of single-incision slings against conventional MUS is uncertain.	1a
Operating times for insertion of single-incision MUSs are shorter than for standard retropubic slings.	1b
Blood loss and immediate postoperative pain are lower for insertion of single-incision slings compared with conventional MUS.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional MUS.	1b
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, there is conflicting evidence regarding sexual function following SUI surgery.	2a
Improvement in sexual function appears higher with single-incision slings than with standard MUS.	1a

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure device, and although this device is no longer available, it is, however, still included in many systematic reviews and meta-analyses.

Recommendations	**Strength rating**
Offer a mid-urethral sling (MUS) to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Inform women that long-term outcomes from MUS inserted by the retropubic route are superior to those inserted via the transobturator route.	Strong
Inform women of the complications associated with MUS procedures and discuss all alternative treatments in the light of recent publicity surrounding surgical mesh.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong

4.2.4.3.2.6 Other treatments for uncomplicated stress urinary incontinence

Intravesical balloon treatment has been explored for women with SUI. The Vesair® gas-filled intravesical balloon differs from other treatment methods in that it is not intended to increase outlet resistance or minimise urethral hypermobility but to attenuate the fluctuation of intravesical pressure when the abdominal pressure increases [427, 428]. Two sham-controlled RCTs have evaluated the Vesair® intravesical balloon [427, 429]. Both reported significant reductions in incontinence symptoms and pad weight but QoL was not significantly different between study arms. High levels of adverse events were reported in both trials as well as significant numbers of withdrawals/device removals. The most common adverse events were dysuria, urgency, gross haematuria and UTIs.

Mechanical devices have been used to treat SUI for centuries. There are several devices available which act either by supporting the bladder neck or urethra to address urethral hypermobility, or by occluding the urethral lumen. A 2014 Cochrane review of eight RCTs that included three small trials comparing mechanical devices to no treatment found inconclusive evidence of benefit [430]. Another 2014 review of mechanical devices concluded that there was insufficient evidence to support their use in women [431]. The place of mechanical devices in the management of SUI remains in question. Currently, there is little evidence from controlled trials on which to judge whether their use is better than no treatment, and large well-conducted trials are required for clarification. There is also insufficient evidence in favour of one particular device and few comparisons of mechanical devices with other forms of treatment [430].

Systematic reviews support the use of compression devices such as the adjustable compression therapy and artificial urinary sphincter (AUS) devices [432, 433]. Although these procedures are largely reserved for those with recurrent or complicated SUI (see Section 4.2.4.3.3.3 External compression devices), these recent additions to the literature include the use of some compression devices for uncomplicated SUI.

4.2.4.3.2.6.1 Summary of evidence and recommendations for other treatments for uncomplicated stress urinary incontinence

Summary of evidence	**LE**
Vesair® intravesical pressure-attenuating balloon improves SUI compared to sham control at 3 months.	1b

Vesair® intravesical pressure-attenuating balloon is associated with significant levels of adverse events.	1b
Implantation of an artificial sphincter can improve or cure incontinence in women with uncomplicated SUI.	3
Implantation of the adjustable compression therapy (ACT®) device may improve uncomplicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the ACT©.	3

Recommendations	Strength rating
Offer Vesair® intravesical balloon to women with mild-to-moderate stress urinary incontinence (SUI) who fail conservative treatment only as part of a well-conducted research trial.	Weak
Offer mechanical devices to women with mild-to-moderate SUI who fail conservative treatment only as part of a well-conducted research trial.	Strong
Inform women receiving artificial urinary sphincter or adjustable compression device (ACT®) that, although cure is possible, even in expert centres there is a high risk of complications, mechanical failure or a need for explantation.	Strong

4.2.4.3.3 Surgery for women with complicated stress urinary incontinence

This section addresses surgical treatment for women with complicated SUI as defined in Section 4.2.2.

Women with associated genitourinary prolapse are included in Section 4.7.

The principal procedures included are:

- Colposuspension or MUS (synthetic or autologous) following failed primary SUI surgery;
- External compression devices: adjustable compression therapy (ACT®) and AUS;
- Adjustable slings.

4.2.4.3.3.1 Colposuspension or mid-urethral sling (synthetic or autologous) following failed primary stress urinary incontinence surgery

Urinary incontinence following SUI surgery may indicate persistent or recurrent SUI, or the development of *de novo* UUI, or both. Careful evaluation including urodynamics is an essential part of the work-up of these patients.

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients are usually too small to allow meaningful comparisons. This means that no firm recommendations can be made regarding which modality is best for the treatment of recurrent SUI, and previous SRs have commented that in view of the absence of any evidence, clinicians must rely largely on expert opinion or personal experience when advising patients about treatment options [434].

The ESTER network meta-analysis revealed that women with transobturator MUS were more likely to undergo repeat surgery than those who had retropubic MUS, and fewer repeat operations were observed after retropubic MUS compared with other interventions [382]. A recent update of two Urinary Incontinence Treatment Network trials [435] compared the retreatment-free survival rates by initial surgical procedure. Five-year retreatment-free survival rates were 87%, 96%, 97%, and 99% for Burch colposuspension, autologous fascial sling, transobturator, and retropubic MUS, respectively. Types of surgical retreatment included autologous fascial sling (19), bulking agent (18), and synthetic sling (1). This suggests that MUS may not be preferred in cases of recurrent SUI [435]. In these cohorts, 6% of women after standard anti-incontinence procedures were retreated within five years; mostly with injection therapy or autologous fascial sling. Not all women with recurrent SUI chose surgical retreatment.

A 2019 Cochrane review attempted to summarise the data regarding different types of MUS procedures for recurrent SUI after failure of primary surgical therapy [436]. The literature search identified 58 records but all were excluded from quantitative analysis because they did not meet eligibility criteria. Overall, there were no data to recommend or refute any of the different management strategies for recurrent or persistent SUI after failed MUS surgery. Another SR looking at the effectiveness of MUS in recurrent SUI included twelve studies and reported an overall subjective cure rate following MUS for recurrent SUI after any previous surgery of 78.5% at an average 29 months' follow-up [437]. The subjective cure rate following MUS after previous failed MUS was 73.3% at follow-up of sixteen months. The authors commented that there was a lower cure rate with

transobturator compared to the retropubic tape for recurrent SUI after previous surgery. Conflicitng evidence comes from a SR assessed the effectiveness and complications of various surgical procedures for female recurrent SUI and reported on data from 350 women in ten RCTs with a mean follow-up of 18.1 months [438]. The authors found no difference in patient-reported and objective cure/improvement rates between retropubic and transobturator MUS in the setting of recurrent SUI. There was also no significant difference between Burch colposuspension and retropubic MUS in terms of patient-reported improvement or objective cure/improvement.

A SR of older trials of open surgery for SUI suggested that the longer-term outcomes of repeat open Burch colposuspension may be poor compared to autologous fascial slings [439]. Similarly, one large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for autologous fascial sling [440].

4.2.4.3.3.1.1 Summary of evidence for surgery in those with recurrent stress urinary incontinence following failed primary surgery

Summary of evidence	**LE**
Failure rates of single-incision slings appear higher than with other types of MUS.	1a
The incidence of repeat surgery is higher in those women who underwent primary transobturator compared to retropubic MUS.	1a
The five-year failure rate of Burch colposuspension appears higher than for synthetic or traditional sling procedures.	2b
Some studies suggest that retropubic synthetic MUS procedures appear to be more effective than transobturator MUS for the treatment of recurrent SUI, but this is not a consistent finding in the literature.	1a
Most procedures are less effective when used as second-line procedures.	2a
Burch colposuspension has similar short-term patient-reported or objective cure rates when compared to TVT for treatment of recurrent SUI.	1b
Autologous sling appears superior to Burch colposuspension for treatment of recurrent SUI.	2b

4.2.4.3.3.2 Adjustable slings

Although adjustable slings are most commonly used for treatment of complicated SUI, they may also be considered for uncomplicated SUI. There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definitions. Few studies have included sufficient numbers of patients or have long enough follow-up to provide useful evidence.

One adjustable sling is the Remeex system (Neomedic International®, Terrassa, Spain), which was investigated in a prospective study of 230 women with SUI [441]. After a mean follow-up of 89 months, 165 patients were cured of SUI (71.7% in the intention-to-treat [ITT] analysis, 80.5% in per protocol [PP] analysis). Forty patients remained incontinent (17.4% in ITT, 19.5% in PP). Eighty-eight patients required readjustment of the sling during follow-up.

The tension was increased in 82 cases due to recurrence of SUI and reduced in six due to outlet obstruction. The currently available adjustable sling devices have differing designs, making it difficult to draw general conclusions about them as a class of procedure.

4.2.4.3.3.2.1 Summary of evidence for adjustable slings

Summary of evidence	**LE**
There is only low level evidence to suggest that adjustable MUS devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard MUS.	4

4.2.4.3.3.3 External compression devices

External compression devices are usually used for treatment of recurrent SUI after failure of previous surgery but can be considered for primary treatment. Studies have largely included patients with profound intrinsic failure of the sphincter mechanism, characterised by low VLPP or urethral closure pressure [432, 433]. The two

intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT®) device and AUS.

ACT®: Using US or fluoroscopic guidance, the ACT® device is inserted by placement of two inflatable spherical balloons; one on either side of the bladder neck. The volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. A SR including eight studies published between 2007 and 2013 with follow-up of one to six years revealed 15–44% of patients considered that their SUI had been cured and 66–78.4% were satisfied [432]. The explantation rate was 19–31%. In these studies, a significant reduction in the number of pads used daily was consistently observed after ACT® balloon placement and QoL was significantly improved. The authors concluded that ACT® balloons constitute a reasonable, minimally-invasive alternative for treatment of female SUI due to intrinsic sphincter deficiency, especially in patients who have already experienced failure of standard surgical treatment.

AUS: The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [430]. There have been a few case series of AUS in women, with populations of 45–215 patients and follow-up of one month to 25 years [442-445]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cure in 59–88%. Common adverse effects included mechanical failure requiring revision (≤ 42% at ten years) and explantation (5.9–15%). In a retrospective series of 215 women followed-up for a mean six years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [445].

Early reports of laparoscopically implanted AUS do not have sufficient patient populations or sufficient follow-up to be able to draw any conclusions [446, 447].

A more recent SR included seventeen studies but all were retrospective or prospective non-comparative case series [433]. Most patients had undergone at least one anti-incontinence surgical procedure prior to AUS implantation (69.1–100%). Outcomes revealed that complete continence rates were 61–100%. The rates of explantation were 0–45%, erosion rates were 0–22% and mechanical failure rates were 0–44%. The authors concluded that AUS can provide excellent functional outcomes in women with SUI resulting from intrinsic urethral sphincter deficiency but at the cost of high morbidity.

4.2.4.3.3.3.1 Summary of evidence for external compression devices

Summary of evidence	**LE**
Implantation of an artificial sphincter improves or cures incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the AUS device may improve complicated SUI.	3
Implantation of the ACT® device may improve complicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and ACT®.	3
Explantation of AUS is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

4.2.4.3.3.4 Recommendations for complicated stress urinary incontinence

Recommendations	**Strength rating**
Management of complicated stress urinary incontinence (SUI) should only be offered in centres with appropriate experience (see Section: 4.2.4.3.1).	Strong
Base the choice of surgery for recurrent SUI on careful evaluation, including individual patient factors and considering further investigations such as cystoscopy, multichannel urodynamics, as appropriate.	Strong
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as second-line treatment, is generally inferior to its use as first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Only offer adjustable mid-urethral sling as primary surgical treatment for SUI as part of a structured research programme.	Strong

Consider secondary synthetic sling, bulking agents, colposuspension, autologous sling or artificial urinary sphincter (AUS) as options for women with complicated SUI.	Weak
Inform women receiving AUS or ACT® device that, although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Strong

4.2.4.3.4 Surgery for stress urinary incontinence in special patient groups

4.2.4.3.4.1 Stress urinary incontinence surgery in obese women

There is no agreement about the outcome of incontinence surgery in obese women. Secondary analysis of an RCT on retropubic and transobturator tapes for treatment of women with SUI suggests that obese women experience inferior outcome compared to non-obese women. Stratification of patients according to BMI (< 30 and ≥ 30) shows a significant difference in objective dry rates (negative pad test) at one year (85.6% vs. 67.8%) and five years (87.4% vs. 65.9%) and subjective cure (absence of SUI symptoms) at one year (85.8% vs. 70.7%) and five years (76.7% vs. 53.6%). At one and five years, 6.7% and 16.3% of patients who were initially dry (negative pad test) after surgery developed a positive pad test [448, 449].

Conversely, short-term outcome of single-incision MiniArc® sling showed comparable objective cure rates (negative cough stress test) at two years (86% and 81% in non-obese and obese women, respectively); similar improvement of the Urinary Distress Inventory 6 and Incontinence Impact Questionnaire seven was observed in non-obese and obese women [450].

4.2.4.3.4.2 Stress urinary incontinence surgery in elderly women

Age appears to be a significant factor in outcome from SUI surgery but there is conflicting evidence. An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 years [451]. An RCT assessing risk factors for the failure of TVT vs. transobturator tension-free vaginal tape (TVT-O) in 162 women also found that age was a specific risk factor for recurrence at one year [452]. In addition, based on a sub-analysis of a trial cohort of 655 women at two years' follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up, were less likely to report objective or subjective improvement in stress and UUI, and were more likely to undergo retreatment for SUI. There was no difference in time to postoperative normal voiding [453].

Another RCT comparing immediate TVT vs. no surgery (or delayed TVT) in older women, confirmed efficacy of surgery in terms of QoL and satisfaction, but with more complications in the surgical arm [454]. Conversely, a cohort study of 181 women undergoing TVT-O found that women aged > 70 years had similar outcomes when compared to women < 70 years in terms of cure rates (92.5% vs. 88.3%), voiding dysfunction, vaginal erosion and groin pain at a median follow-up of two years [455].

Furthermore, a SR of the efficacy of treatments of UI in older patients suggests that MUS is successful in older patients (≥ 65 years) with 5.2–17.6% reporting persistent SUI after surgery. No difference in the frequency of *de novo* UUI, persistent UUI or persistent SUI was found in older patients [384].

A cohort study of 256 women undergoing vagina-to-skin (inside-out) TOT reported similar efficacy in older vs. younger women, but there was a higher risk of *de novo* urgency in older patients [456].

4.2.4.3.4.3 Summary of evidence and recommendations for stress urinary incontinence surgery in special patient groups

Summary of evidence	**LE**
Incontinence surgery may be safely performed in obese women, however, outcomes may be inferior.	1
The risk of failure from surgical repair of SUI, and the risk of suffering adverse events, appears to increase with age.	2b
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendations	**Strength rating**
Inform obese women with stress urinary incontinence (SUI) about the increased risks associated with surgery, together with the lower probability of benefit.	Weak
Inform older women with SUI about the increased risks associated with surgery, together with the likelihood of lower probability of benefit.	Weak

*4.2.5 **Follow-up***

The follow-up of patients with SUI is dependent on the treatment given. For conservative and physical therapies, sufficient time should be allowed for the demonstration of a therapeutic effect. For pharmacological treatment, early follow-up is recommended. For most surgical interventions, short-term follow-up should be arranged to assess efficacy and identify any early postoperative complications.

The Panel is supportive of long-term outcome assessment via registries and recognises the paucity of high-quality long-term data, specifically regarding complications from surgery.

4.3 Mixed urinary incontinence

The term MUI is broad because it may refer to equal stress and urgency symptoms, stress-predominant symptoms, urgency-predominant symptoms, urodynamic stress urinary incontinence (USUI or USI) with DO or USUI with clinical urgency symptoms, but no DO [457]. The challenge of this broad definition is that it leads to inconsistencies when evaluating treatment options and outcomes.

*4.3.1 **Epidemiology, aetiology and pathophysiology***

The prevalence rates of MUI vary widely in the literature. Most epidemiological studies have either not considered subtypes of UI, or only reported on SUI, UUI and MUI. The current literature is unclear regarding the population prevalence and risks for the different UI subtypes [458]. There are many urinary symptom questionnaires used in epidemiological research, with varying evidence of validity. Caution is needed when comparing epidemiological studies that do or do not report a separate MUI subgroup, and when generalising from population level data to clinical practice. The problems arise from significant heterogeneity in terms of types of questionnaires/surveys used, population parameters, variable response rates, varying definitions of MUI, and outcome measures.

It seems apparent, however, that MUI is the second most common form of UI, after SUI, with most studies reporting a 7.5–25% prevalence [458]. One can extrapolate that among women with UI, approximately one-third have MUI [459]. In a secondary analysis of a large clinical trial, 655 women were evaluated for UI and their response to treatment [460]. It was found that 50–90% of women fell into the category of MUI based on patient-reported answers to the Medical Epidemiologic and Social Aspects of Aging and Urinary Distress Inventory (UDI) questionnaires. However, when objective criteria such as urodynamic findings were used, only 8% of women were categorised as having MUI.

Mixed urinary incontinence is usually caused by a combination of the same factors that cause SUI and UUI. Several factors may be responsible for its development, including oestrogen deficiency, abnormalities in histomorphology, and microstructural changes [461]. One report postulates that an incompetent sphincter and bladder neck allow urine to enter the proximal urethra during stress, causing a urethro-detrusor reflex that triggers involuntary detrusor contraction, which then causes urgency and UUI [462]. Another study has shown that urine flow across the urethral mucosa increases the excitability of the micturition reflex [463]. Ultimately, it is unlikely that one theory or risk factor can explain the development of MUI and its symptoms; it is more probable that disturbances in several elements and the lack of bladder compensation results in the development of MUI [461].

*4.3.2 **Diagnostic evaluation***

Assessment of patients with MUI begins with a thorough history of the patient's urinary symptoms and follows the recommendations set out in the general evaluation and diagnosis of LUTS section 3. It is conventional to try and categorise MUI as either stress or urge predominant.

Mixed urinary incontinence is difficult to diagnose, as the condition comprises many phenotypes. Some women exhibit detrusor contractions provoked by physical stressors, some have unprovoked detrusor contractions, and many have no abnormal detrusor contractions, but still report urine leakage with the sensation of urgency. Some women with urgency symptoms do not manifest UUI because their urethral sphincter is strong and often able to prevent urine leakage [464].

The role of urodynamics in MUI is unclear, but establishing objective degrees of SUI and DO incontinence may help in counselling patients about the most appropriate initial treatment option.

4.3.2.1 Summary of evidence and recommendations for the diagnosis of mixed urinary incontinence

Summary of evidence	LE
There is no evidence that urodynamics affects outcomes of treatment for MUI.	3

Recommendations	Strength rating
Complete a thorough history and examination as part of the assessment of mixed urinary incontinence (MUI).	Strong
Characterise MUI as either stress-predominant or urgency-predominant where possible.	Weak
Use bladder diaries and urodynamics as part of the multimodal assessment of MUI to help inform the most appropriate management strategy.	Strong

4.3.3 ***Disease Management***

4.3.3.1 Conservative management

Women with MUI generally have more severe symptoms and respond less well to treatment than women with only SUI or UUI [465]. Clinicians are encouraged to begin treatment for MUI with conservative management directed toward the most bothersome component of the symptom spectrum and to reserve surgery as a last resort [464].

4.3.3.1.1 Pelvic floor muscle training

An RCT comparing PFMT with and without an audiotape for 71 women with UI did not find any difference between the two treatment arms [466]. Mean number of incontinent episodes per day decreased from 3.9 overall to 3.2 for participants with MUI. Six months after completing the course of exercises, approximately one third of all enrolees reported that they continued to note good or excellent improvement and desired no further treatment.

A small RCT including 34 women with SUI and MUI compared eight weeks of PFMT with no treatment and found that PFMT significantly increased PFM strength, improved QoL, and reduced the frequency of UI episodes compared to no treatment [467]. Another RCT including SUI and MUI confirmed these results [468].

A multicentre randomised controlled non-inferiority trial on 467 women with MUI was conducted in ten hospitals. Participants were randomised 1:1 to receive EA (36 sessions over twelve weeks with 24 weeks of follow-up) or PFMT–solifenacin (5 mg/day) over 36 weeks. In women with moderate-to-severe MUI, EA was not inferior to PFMT–solifenacin in decreasing the 72-h incontinence episodes (between-group difference, –1.34%) [469].

In a comparative study of the effectiveness of behavioural therapy and PFMT (combined with MUS vs. sling alone in women with MUI), 416 (86.7%) had post-baseline outcome data and were included in primary twelve-month analyses [470]. The UDI score in both groups significantly decreased (178.0 to 30.7 points in the combined group, 176.8 to 34.5 points in the sling-only group). The model-estimated between-group difference, did not meet the minimal clinically important difference threshold. Adherence to the behavioural therapy and PFMT regimes, which is a prerequisite for achieving a satisfacory outcome, was not reported in the study.

A Cochrane review comparing PFMT with no or sham treatment included 31 RCTs from fourteen countries, but there was only one study including women with MUI and one with UUI and none of them reported data on cure, improvement, or number of episodes of these subgroups [341].

Another Cochrane review comparing different approaches to delivery of PFMT (21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [345]. This concurs with the latest ICI publication [347]. No other consistent differences between techniques were found.

The effect of combining biofeedback with PFMT has already been fully addressed in Section 4.2.4.1.3, and there was no evidence of any additional benefit in a population with predominantly MUI.

4.3.3.1.2 Bladder training

Details on BT programmes are given in Section 4.2.4. The ICI 2017 [347] concluded that for women with UUI or MUI, PFMT and BT are effective first-line conservative therapies. One RCT assigned 108 women with diagnoses of SUI (n = 50), UUI (n = 16), or MUI (n = 42) to sixth weeks of BT and PFMT or BT alone [471].

Overall, and in the SUI and MUI subgroups, significantly more patients in the BT and PFMT group reported cure and improved symptoms.

4.3.3.1.3 Electrical stimulation

A Cochrane review on ES for SUI included participants with SUI or stress-predominant MUI. Twenty-five percent of the included trials were deemed to have a high risk of bias due to a variety of factors, including baseline differences between groups and industry funding. For subjective cure or improvement of SUI, low-quality evidence indicated that ES was better than no active treatment or sham treatment. Electrical stimulation for OAB and SUI is covered in Sections 4.1.4.1.5.4 and 4.2.4.1.3.2.

4.3.3.2 Summary of evidence and recommendations for conservative management in mixed urinary incontinence

Summary of evidence	**LE**
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Pelvic floor muscle training is better than no treatment for improving UI and QoL in women with MUI.	1a
Bladder training combined with PFMT may be beneficial in the treatment of MUI.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer bladder training as a first-line therapy to adults with MUI.	Strong
Offer supervised intensive pelvic floor muscle training, lasting at least three months, as a first-line therapy to all women with MUI (including elderly and postnatal women).	Strong

4.3.3.3 Pharmacological management

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

4.3.3.3.1 Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI but not SUI, suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [472]. In another study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [473]. Similar results were found for solifenacin [474, 475].

4.3.3.3.2 Duloxetine

In one RCT of duloxetine vs. placebo, 588 women were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups, although results in the stress-predominant groups were better [476]. Treatment-emergent adverse event rate in the duloxetine group was 61.3% with discontinuation rates of 15.7%. Adverse event rates were higher in those participants taking other concomitant antidepressant agents.

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations but no adverse events data were reported [477].

4.3.3.3.3 Summary of evidence and recommendations for pharmacological management of mixed urinary incontinence

Summary of evidence	**LE**
Limited evidence suggests that anticholinergic drugs are effective for improvement of the UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and MUI symptoms, but adverse event rates are high.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI.	Strong

Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Weak

4.3.3.4 Surgical management

The surgical treatment options for MUI, include all the anti-incontinence procedures are outlined in the SUI Section 4.2.4.3.

Many RCTs include patients with pure SUI or pure UUI as well as patients with MUI. However, few RCTs report separate outcomes for MUI subgroups.

Post hoc analysis of a large RCT showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of preoperative urgency [453]. A similar *post hoc* review of another RCT comparing transobturator and retropubic MUS showed that the greater the severity of preoperative urgency, the more likely that treatment would fail [97]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO). Another RCT including 93 patients with MUI showed a significant improvement in continence and QoL in the group that had TVT and botulinum toxin A (Botox®) rather than with either treatment alone [478].

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing MUS insertion, overall satisfaction rates were lower for women with mixed symptoms and DO on preoperative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [479]. A comparison of two parallel cohorts of patients undergoing Burch colposuspension for SUI, with and without DO, found inferior outcomes in women with MUI [480].

One cohort of 450 women, showed that in urgency-predominant MUI, the success rate of TVT fell to 52% compared to 80% in stress-predominant MUI [481]. In a study of 1113 women treated with transobturator TVT, SUI was cured equally in stress- or urgency-predominant MUI. However, women with stress-predominant MUI had significantly better overall outcomes than women with urgency-predominant MUI [482].

In contrast to studies examining older surgical methods, more recent studies (generally small case series) have reported that UUI symptoms improve in 30–85% of women with MUI after MUS surgery [483].

In a prospective, multicentre, comparative trial, 42 women who had TVT for MUI had greater improvement in urgency and QoL scores than 90 women who had TOT. There were no significant differences in the cure and satisfaction rates between the two groups [484].

In a single-centre prospective study, 86 consecutive women underwent TOT for MUI. At a mean follow-up of 59 months, SUI was cured objectively in 83.7% and subjectively in 87.2% of the patients. The continence rates were 74.4% for UUI and 66.3% for MUI (cure of both components). The patient-reported success rate was 87.2% (“much better” or “very much better” on the Patient Global Impression of Improvement scale). There were significant improvements in all domains except general health. The univariate analysis found no significant risk factor for persistence of SUI. Median age > 60 years and menopause were predictive for persistence of UUI. Median and mean age > 60 years were predictive of persistence of overall incontinence [485]. Overall, the outcome for women with pre-existing UUI remains uncertain.

In a secondary analysis of a study of transobturator TVTs in the treatment of women with urodynamic MUI, no difference in patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to vagina (outside-in) groups (63.2% and 65.5%, respectively) at nine years’ follow-up [421].

Analysis of the trial populations included in the meta-analysis on single-incision slings suggests that the evidence can be generalised to women who have predominantly SUI, and no other clinically severe LUT dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI.

Research trials should define accurately what is meant by MUI. There is a need for well-designed trials comparing treatments in populations with MUI, and in which the type of MUI has been accurately defined.

4.3.3.4.1 Summary of evidence and recommendations for surgery in patients with mixed urinary incontinence

Summary of evidence	LE
Women with MUI are less likely to be cured of their UI by SUI surgery than women with SUI alone.	2
The response of pre-existing urgency symptoms to SUI surgery is unpredictable.	1b

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Warn women that surgery for MUI is less likely to be successful than surgery for stress urinary incontinence alone.	Strong
Inform women with MUI that one single treatment may not cure urinary incontinence; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	Weak

4.4 Underactive bladder

Underactive bladder is a common clinical entity, defined by the ICS as *"a symptom complex characterised by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms"* [486]. Diagnosis of UAB is based on clinical symptoms and the presentation and aetiology can be variable.

This differs from DU, which is a diagnosis based on urodynamic studies. Detrusor underactivity is defined by the ICS as *"a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"* [1]. Acontractile detrusor is specified when there is no detrusor contraction.

Female voiding dysfunction is defined by the ICS as a diagnosis based on symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or abnormally high PVR volume; ideally on repeated measurement to confirm abnormality. Pressure–flow studies may be required to determine the cause of the voiding dysfunction [31].

*4.4.1 **Epidemiology, aetiology, pathophysiology***

4.4.1.1 Epidemiology

Underactive bladder as an entity remains difficult to study, partly because its corresponding urodynamic correlate, DU, remains loosely defined, leading to significant variability in diagnostic criteria across research studies and significant overlap of symptoms with other conditions. As a consequence of the variable definition, reported prevalence also varies and ranges from 12% to 45% in women, with increased prevalence seen with age [76] and in institutionalised elderly women [487].

Several studies have demonstrated similar prevalence rates for DU in the ambulatory setting of around 12–19.4% [488-490]. As would be expected, voiding symptoms consistent with UAB are higher. A Detroit population study surveyed 291 women, with 20% reporting difficulty with bladder emptying [491]. In a large cross-sectional, population-based internet survey conducted in the USA, UK and Sweden including 15,861 women aged ≥ 40 years, 20.1% referred to weak flow, 27.4% to incomplete bladder emptying and 38.3% to terminal dribbling [5].

Some studies have identified the coexistence of DO during filling and DU in the voiding phase of urodynamic studies (formerly known as detrusor hyperactivity with impaired contractility; DHIC) as a common finding in elderly women. Up to 38.1% of incontinent institutionalised women showed DHIC in urodynamic studies [492, 493].

4.4.1.2 Aetiology

The presence of DU in diverse clinical groups suggests multifactorial aetiology [494]. Idiopathic DU is probably partly an age-dependent decrease in detrusor contractility with no other identifiable causes, but young women can also have DU. There are many secondary causes of DU, including neurogenic (e.g., multiple sclerosis, multiple systemic atrophy, spinal cord injury, spina bifida, Parkinson's disease, hydrocephalus, transverse myelitis, stroke, Guillain–Barré syndrome, diabetes mellitus, and pelvic nerve injury), myogenic (acute prolonged bladder overdistension, diabetes mellitus, and BOO) and iatrogenic (pelvic surgery) causes [495].

4.4.1.3 *Pathophysiology*

There are many pathways involved in normal detrusor contraction, and there are different possible sites of dysfunction [76] with a variety of mechanisms involved in UAB:

- Central circuits and centres (prefrontal cortex, periaqueductal gray, pontine micturition centre and hypothalamus): failure of integration or processing;
- Efferent pathways (sacral cord, sacral nerves, pelvic nerves and postganglionic neurons): impaired detrusor activation;
- Afferent pathways (peripheral afferent nerves, anterolateral white column and posterior column): early termination of voiding reflex;
- Muscle (detrusor myocytes and extracellular matrix): loss of intrinsic contractility.

Different aetiologies can share common pathophysiological mechanisms: for example, diabetes mellitus affects mainly afferent pathways and the detrusor muscle; and neurogenic diseases affect central circuits and efferent/ afferent pathways.

One study suggests that in patients with DU, there is significant urothelial dysfunction, increased sub-urothelial inflammation and apoptosis, and altered sensory protein expression [496]. Impaired urothelial signalling and sensory transduction pathways may reflect part of the pathophysiology of DU. Pelvic ischaemia is another proposed mechanism of DU in ageing patients [496] (Figure 1).

Figure 1: Management and treatment of women presenting with urinary incontinence, site of dysfunction, major aetiological factors, mechanisms

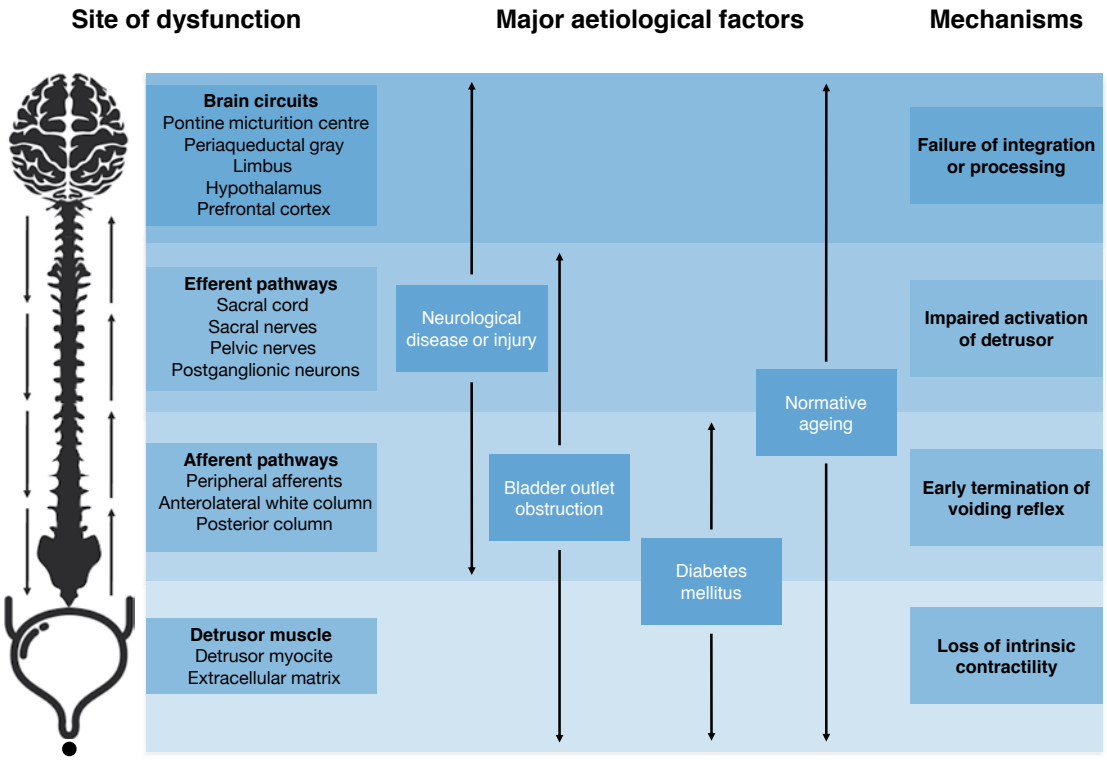


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4.4.2 ***Classification***

There is no current classification system of UAB. Patients can be classified according to presumed aetiology or pathogenic mechanism, but without sufficient longitudinal data or high-level evidence to establish prognostic factors, the classification of UAB patients in terms of relevant clinical characteristics or risk of complications is not possible.

4.4.3 ***Diagnostic evaluation***

4.4.3.1 *Symptoms associated with detrusor underactivity*

A retrospective study correlated LUTS with urodynamic findings in 1788 patients (1281 women). Women with DU, defined as detrusor pressure at maximum flow rate ($P_{det}Q_{max}$) < 20 cmH_2O, maximum flow rate (Q_{max}) < 15 mL/s, BVE < 90% and excluding obstruction on video-urodynamic studies, had a significantly higher

occurrence of reduced and/or interrupted stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, and absent and/or decreased sensation compared with women with normal pressure and flow [497]. A qualitative study on a small sample of male and female patients diagnosed with DU reported a variety of LUTS and associated impact on QoL. Storage symptoms of nocturia, increased daytime frequency, and urgency, and the voiding symptoms of slow stream, hesitancy, and straining were reported by over half of the patients. A sensation of incomplete emptying and post-micturition dribble were also frequently described. The impact of their symptoms on QoL was variable, but in general, storage symptoms were more bothersome [498].

Based on current data, it is not possible to find a pivotal symptom or collection of symptoms to identify DU patients. The ICI Questionnaire Underactive Bladder (ICIQ UAB) has been developed as a research PROM tool, that needs validation before use in common clinical practice [499].

4.4.3.2 Urodynamic studies

Non-invasive studies like uroflowmetry, PVR volume measurement and BVE determination are potentially useful to identify women who might have DU. There is considerable symptomatic overlap with BOO, and uroflowmetry and PVR volume findings may also be similar. Only invasive urodynamics with pressure–flow studies can reliably distinguish DU from BOO and these urodynamic diagnoses can coexist. Diagnosis in women is particularly difficult as they can void by relaxing the pelvic floor, that is, without detectable detrusor contraction during pressure–flow study and without increased abdominal pressure [500]. The simplest methods to define and diagnose DU are based on the use of cut-off values of Q_{max} and $P_{det}Q_{max}$, possibly combined with cut-off values of PVR volume and BVE. However, there is no consensus on which cut-off values should be used [501]. It is obvious that the prevalence of DU depends on the criteria used. In a retrospective study of 1015 women, DU was found in 14.9% when using Q_{max} < 12 mL/s or PVR volume > 150 mL; in 9.6% when using $P_{det}Q_{max}$ < 30 cm H_2O and Q_{max} < 10 mL/s; and in 6.4% when using $P_{det}Q_{max}$ < 20 cm H_2O, Q_{max} < 15 mL/s and BVE < 90% [502].

More elaborate methods combine urodynamic data into an index or a physical quantity that reflects bladder contraction strength. A value below a certain threshold would thus diagnose DU. Again, there is no consensus regarding what is normal/abnormal. Table 4 provides an overview of the best-known parameters, their background, and typical values. Watt's factor (WF) estimates the power generated by the detrusor per unit area of bladder surface [503] and it varies during voiding. Usually, WF_{max} is considered. Alternatively, its value at Q_{max} can be used. Projected isovolumetric pressure (PIP) is a gross simplification of the bladder output relation and estimates the maximum detrusor pressure that can be generated by the bladder when the outlet is closed; the isovolumetric detrusor pressure. The bladder contractility index (BCI) is simply a reduction of PIP to an index [504]. The population in which PIP and BCI were developed mainly consisted of men. Projected isovolumetric pressure one, is similar to PIP and also estimates the isovolumetric detrusor pressure, but was developed in an entirely female population via an experimental method [505].

A third method of quantifying bladder contraction strength involves stop tests. One study compared three types of direct measurement of isovolumetric pressure: (1) the voluntary stop test, in which the patient voluntarily interrupted flow; (2) the mechanical stop test, in which flow was interrupted by a balloon catheter; and (3) the continuous occlusion test, in which the subject tried to void against a blocked outlet. The latter had the best reliability and best detected drug-induced changes, though the results of the mechanical stop tests were similar [506].

All parameters discussed above give some information about the strength of detrusor contraction in a given void. They do not necessarily reflect what the detrusor might potentially achieve under optimum conditions [507]. Also, they give no information on the important aspect of voiding duration. No parameters for this are available. Finally, abnormally low bladder contraction strength does not necessarily imply insufficient bladder contraction strength to achieve optimal voiding. Table 4 summarises different parameters to measure detrusor contraction in female patients.

Table 4: Most used parameters to measure detrusor contraction in female patients

Parameter	Basis	Population	Values
Watt's factor (WF) [503]	Hill equation of muscle contraction in a spherical organ, with fixed constants obtained from experimental and clinical studies	Eight asymptomatic female volunteers aged 28–45 years (median 34 years)	Ideal voiding (bell-shaped flow curves): WF_{max} 11-24 W/m^2 Non-ideal voiding: WF_{max} 5–10 W/m^2 Normally WF_{max} > 7 W/m^2 (expert opinion, unspecified population) [508]
Projected isovolumetric detrusor pressure (PIP, cm H_2O) and Bladder Contractility Index (BCI), using PIP as an index [504, 509]	Bladder Output Relation, simplified to a straight line with fixed slope of 5 cm H_2O/mL/s (Formula: $P_{det}Q_{max}$ + 5xQ_{max})	Unspecified population, mainly men with BPO	Classification based on expert opinion: > 150: strong contraction 100-150: normal contraction 50-100: weak contraction < 50: very weak contraction
Projected isovolumetric detrusor pressure 1 (cm H_2O) [505]	Comparison of Q_{max} and $P_{det}Q_{max}$ values with stop test results (Formula: $p_{det}Q_{max}$ + Q_{max})	100 women with UUI aged 53–89 (mean: 70) years	5th-95th percentile: 29–78 cm H_2O Mean: 49 cm H_2O Median: 48 cm H_2O Proposed typical values: 30-75 cm H_2O
Continuous occlusion test [506]	Direct measurement of isovolumetric voiding contraction	70 women with UUI aged 53–89 (mean: 70) years	Mean ± SD: 48.7 ± 24.4 cm H_2O

BPO = benign prostatic obstruction; BCI = Bladder contractility index; PIP = Projected isovolumetric pressure; UUI = urgency urinary incontinence; WF = Watt's factor.

*4.4.4 **Disease management***

As there are so many different possible causes and pathogenic mechanisms involved in female UAB, preventive and therapeutic strategies are difficult to define. Among preventive strategies, early recognition after major surgery or labour might prevent long-term problems associated with prolonged bladder over-distension. Nerve-sparing techniques for radical pelvic surgery are more favourable in terms of early recovery of bladder function [510, 511].

Treatment of female DU includes strategies to ensure bladder drainage, increase bladder contraction, decrease urethral resistance, or a combination [508]. The management goals for UAB are to improve symptoms and QoL, to reduce the risk of complications for impaired bladder emptying, and to identify situations where interventions may not be appropriate.

4.4.4.1 Conservative management

4.4.4.1.1 Behavioural interventions

Regular or timed voiding to avoid bladder over-distension should be encouraged in women with impaired bladder sensations. Assisted voiding by abdominal straining with adequate relaxation of the PFM has been recommended, as well as double or triple voiding in an attempt to improve bladder emptying. None of these manoeuvres has proven its efficacy in a randomised study. There is a possible association between voiding by excessive abdominal straining and the risk of pelvic organ prolapse [512]. A small retrospective study in women with neurogenic acontractile detrusor secondary to spina bifida showed that Valsalva voiding may increase the risk of rectal prolapse compared with CISC [513].

4.4.4.1.2 Pelvic floor muscle relaxation training with biofeedback

There are no RCTs on PFM relaxation training in adult women with UAB. Contradictory to common beliefs, one study found significant relaxation of the PFMs after contraction [514] and another study found that PFM relaxation training over time increased the speed of relaxation after a single contraction [515]. However, muscle contraction is known to be followed by relaxation. There is some evidence from the paediatric literature, including one RCT that compared efficacy of PFM relaxation with biofeedback plus combined therapy (including hydration, scheduled voiding, toilet training and diet) vs. combined therapy alone in children with non-neuropathic UAB and voiding dysfunction. Mean number of voiding episodes was significantly increased in the relaxation training group compared with the group with only combined treatment (6.6 ± 1.6 vs. 4.5 ± 1

times a day). Postvoid residual urine volume and voiding time decreased considerably, whereas maximum urine flow increased significantly in the relaxation group compared with the combined treatment group (17.2 ± 4.7 vs. 12.9 ± 4.6 mL/s) [516].

4.4.4.1.3 Clean intermittent self-catheterisation

See Section 4.1.4.1.3 for details on CISC.

4.4.4.1.4 Indwelling catheter

Indwelling urinary catheter may be an option for some women who have failed all other treatments and are unable to perform CISC. Complications include UTI, stone formation and urethral damage. Suprapubic catheterisation may be preferable over urethral catheterisation to minimise the risk of urethral trauma and pain [517].

4.4.4.1.5 Intravesical electrical stimulation

Intravesical electrical stimulation (IVES) can be used to improve bladder dysfunction by stimulating A-delta mechanoreceptor afferents, but requires preservation of afferent circuits and healthy detrusor muscle. One retrospective study in sixteen patients (eleven females) found that two-thirds of patients with a weak detrusor after prolonged bladder over-distension regained balanced voiding after IVES due to detrusor reinforcement [518].

4.4.4.1.6 Intraurethral insert

The intraurethral insert, or prosthesis, is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. A narrative review [519] that evaluated the InFlow™ intra-urethral valve pump and activator identified seven studies of which six were industry sponsored. The studies reported a high drop-out rate (12–50%), mainly due to tolerability issues (leakage and discomfort), but discontinuation rates were found to be reduced with careful patient education and counselling prior to commencement. Amongst participants who did tolerate the device, QoL rates improved by 60% and UTI rates were marginally lower than for the standard comparator (CISC). The studies reported equivalent efficacy for the insert in terms of reducing PVR compared to CISC. The certainty of evidence from this review remains low due to clinical heterogeneity and publication bias.

4.4.4.2 Pharmacological management

4.4.4.2.1 Parasympathomimetics

Theoretical approaches to UAB pharmacological treatment include direct stimulation of detrusor cell muscarinic receptors using agonists like carbachol or bethanechol, or inhibiting acetylcholinesterase (enzyme that inhibits the endogenous muscarinic agonist acetylcholine) using agents such as distigmine, pyridostigmine or neostigmine.

A SR on the use of parasympathomimetics in patients with UAB included ten RCTs (controls typically received placebo or no treatment). Three studies reported significant improvements relative to the control group, but six did not and one even reported significant worsening of symptoms. There was no evidence for differences between individual drugs, specific uses of such drugs, or in outcome measures [520]. The review concluded that the available studies do not support the use of parasympathomimetics for treating UAB, especially when frequent and/or serious adverse effects (gastrointestinal upset, blurred vision, bronchospasm and bradycardia) are taken into account.

4.4.4.2.2 Alpha-adrenergic blockers

In order to improve bladder emptying, decreasing outlet resistance through sympathetic blockade at the bladder neck/urethra has been investigated. One prospective study with tamsulosin showed similar improvement in terms of uroflowmetry parameters (specifically in the percentage of patients who had a good therapeutic response) in women with BOO (39.4%) or DU (32.7%) [521]. Another longitudinal study including fourteen women with DU showed clinical and urodynamic improvements after tamsulosin [522]. A prospective single-blind RCT in female patients with DU compared efficacy of alpha-blocker, cholinergic drugs or combination therapy, with the latter exhibiting the best results [523].

4.4.4.2.3 Prostaglandins

Prostaglandins are prokinetic agents that promote smooth muscle contraction. Prostaglandins E2 and F2 have been used intravesically to treat urinary retention after surgery. A Cochrane review showed a significant association between intravesically administered prostaglandin and successful voiding among postoperative patients with urinary retention. However, the success rate was low (32%) compared to placebo. It should also be noted that the 95% CI was wide, RCTs included in the pooled analysis were underpowered with

methodological limitations, and the event rate was very low, indicating a very low certainty of the evidence [524]. Intravesical prostaglandin treatment is rarely used and further research is necessary before it can be taken up more widely.

4.4.4.3 Surgical management

4.4.4.3.1 Sacral nerve stimulation

Sacral nerve stimulation is approved by the US FDA for therapy of non-obstructive urinary retention. The mechanism of action has not been fully elucidated, but activation of afferent sensory pathways, modulation–activation of the central nervous system, and inhibition of inappropriate activation of the guarding reflex are some of the mechanisms proposed.

An RCT included 37 patients in the implantation arm and 31 in the standard medical therapy arm, showing a mean decrease in PVR volume in the implantation group compared with a control of 270 mL and a mean increase in voided PVR volume of 104 mL [525]. A meta-analysis of seven studies showed a mean difference in PVR volume reduction of 236 mL and a mean voided volume increase of 299 mL [526]. The response rate during the trial phase ranged from 33 to 90% (mean 54.2%) and the success rate of permanent implantation ranged from 55 to 100% (mean 73.9%), highlighting that patient selection is crucial [527]. A subgroup of women with idiopathic urinary retention (Fowler's syndrome) had a higher response rate of 68–77% [528].

In conclusion, SNS is a valid option for female patients with DU, with proper patient selection. Women should have preserved bladder contractility on urodynamic tests and mechanical/anatomical BOO should be excluded. Patients with evidence of anatomical BOO, suspected loss of intrinsic detrusor contractility or neurogenic bladder dysfunction show lower response rates [529].

4.4.4.3.2 Onabotulinumtoxin A

OnabotulinumtoxinA injections in external striated urethral sphincter may improve voiding in patients with DU by reducing outlet resistance and reducing the guarding reflex. Some retrospective case studies have shown improvement in voiding symptoms, recovery of spontaneous voiding, and improvement in urodynamic parameters (reduction of voiding pressure and/or urethral closure pressures, reduced PVR volume) [530, 531]. The duration of symptomatic relief is short; typically three months.

4.4.4.3.3 Transurethral incision of the bladder neck

Transurethral incision of the bladder neck has been described in short series of women with refractory DU. In a retrospective case study, 40/82 (48.8%) women achieved satisfactory outcomes (spontaneous voiding with voiding efficiency ≥ 50%), but five (6.1%) patients developed SUI and two (2.4%) developed a vesico-vaginal fistula [532].

4.4.4.3.4 Reduction cystoplasty

This is an uncommon procedure with a few case reports described only in men [533].

4.4.4.3.5 Myoplasty

One retrospective multicentre study reported the long-term results of latissimus dorsi detrusor myoplasty in patients with bladder acontractility, with 71% recovering complete spontaneous voiding, with a mean PVR volume of 25 mL [534]. No other groups have published their experience to reproduce these findings.

4.4.4.4 Summary of therapeutic evidence on detrusor underactivity

The level of evidence for most therapeutic interventions for DU is low. Only CISC remains as a gold standard to reduce the adverse consequences of a high PVR volume and incomplete voiding, in spite of the low level of evidence that supports this statement.

4.4.4.4.1 Summary of evidence and recommendations for underactive bladder

Summary of evidence	**LE**
Clean intermittent self-catheterisation has proven efficacy in patients who are unable to empty their bladder.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an enhanced risk of UTI.	3
Intravesical electrical stimulation may be useful in some patients after prolonged bladder over-distension.	3
Intra-urethral inserts/prostheses may be useful in selected patients as an alternative to CISC but existing research has highlighted issues with tolerance, infection and device migration.	2b

Parasympathomimetics do not improve clinical or urodynamic parameters of UAB and frequent and/or serious adverse effects may arise.	1b
There is limited evidence about effectiveness of alpha-adrenergic blockers in women with UAB.	2b
Very low certainty evidence indicates that intravesically administered prostaglandins may promote successful voiding in patients with urinary retention after surgery.	1a
Sacral nerve stimulation improves voided volume and decreases PVR volume in women with DU.	1b
There is limited evidence for the effectiveness of onabotulinumtoxinA external urethral sphincter injections to improve voiding in women with UAB.	3
Transurethral bladder neck incision may improve voiding in women with DU, but complications (SUI, vesico-vaginal fistulae) may appear.	3
There is limited evidence for effectiveness of detrusor myoplasty.	3

Recommendations	**Strength rating**
Encourage double voiding in those women who are unable to completely empty their bladder.	Weak
Warn women with underactive bladder (UAB) who use abdominal straining to improve emptying about pelvic organ prolapse risk.	Weak
Use clean intermittent self-catheterisation (CISC) as a standard treatment in patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of CISC.	Strong
Offer indwelling transurethral catheterisation and suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak
Do not routinely recommend intravesical electrical stimulation in women with UAB.	Weak
Do not routinely recommend parasympathomimetics for treatment of women with UAB.	Strong
Offer alpha-adrenergic blockers before more-invasive techniques.	Weak
Offer intravesical prostaglandins to women with urinary retention after surgery only in the context of well-regulated clinical trials.	Weak
Offer onabotulinumtoxin A external sphincter injections before more-invasive techniques as long as patients are informed that the evidence to support this treatment is of low quality.	Weak
Offer sacral nerve stimulation to women with UAB refractory to conservative treatment.	Strong
Do not routinely offer detrusor myoplasty as a treatment for detrusor underactivity.	Weak

*4.4.5 **Follow-up***

Natural history and clinical evolution at long-term follow-up of women with DU is not well known. No longitudinal cohort studies with long-term follow-up are described in the literature. The interval between follow-up visits depends on patient characteristics, treatments given and the frequency of urinary complications.

4.5 Bladder outlet obstruction

*4.5.1 **Introduction***

Bladder outlet obstruction is defined by the ICS as "*obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate*" [1]. Its precise diagnosis requires urodynamic evaluation including an assessment of pressure and flow.

Voiding dysfunction is a broad term defined by the ICS as *"a diagnosis made by symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or raised PVRs, ideally on repeated measurement to confirm abnormality"* [113]. Pressure–flow studies are required to determine the precise cause of the voiding dysfunction. In women, voiding dysfunction can be caused by BOO or DU [1]. There are also non-obstructive causes and therefore voiding dysfunction and BOO should not be used interchangeably. Another term that must be differentiated from BOO and voiding dysfunction is dysfunctional voiding, which is a specific and discrete form of voiding dysfunction characterised by an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal individuals [113].

*4.5.2 **Epidemiology, aetiology, pathophysiology***

4.5.2.1 Epidemiology

Estimates of prevalence of BOO among women vary from 2.7% to 29% [535]. One large series of women undergoing urodynamic evaluation for LUTS found that ~20% are diagnosed with BOO. The wide variance is due to several factors, including differences in definitions and diagnostic criteria for female BOO, differences in study populations, and variation in study methods. The estimated prevalence rates of LUTS due to BOO in women are lower than those reported in men (18.7–18.9% vs. 24.3–24.7%) [536].

Prevalence of voiding LUTS is associated with age [55, 537, 538], parity [55, 539], prolapse [55, 539] and prior continence surgery [55, 539]. Bladder outlet obstruction has long been postulated to cause mainly voiding symptoms [540] but recent data from a series of 1142 consecutive women referred for evaluation of LUTS suggest that storage symptoms may be predominant in women diagnosed with BOO, and excess daytime urinary frequency was the most common symptom reported by 69% [535].

4.5.2.2 Pathophysiology

Bladder outlet obstruction is one of multiple causes of voiding dysfunction in women. The obstruction can be either anatomical (mechanical) or functional. In anatomical BOO, there is a physical or mechanical obstruction to the outflow of urine, whereas in functional BOO there is a non-anatomical, non-neurogenic obstruction of the outlet usually resulting from non-relaxation of the bladder neck, sphincter or PFM, or increased urethral sphincter tone or PFM contraction during voiding, as observed in patients with dysfunctional voiding.

Mechanisms for anatomical (mechanical) obstruction include external compression, fibrosis, stricture or injury to the urethra and kinking of the urethra due to POP. Progressive fibroblastic reaction around the urethra induced by mesh tapes or slings used in incontinence surgery may also cause anatomical (mechanical) obstruction [495]. In a retrospective review of 192 women diagnosed with BOO, 64% had mechanical obstruction [535].

Functional obstruction may be caused by failure of relaxation, or contraction, of the bladder neck and/or urethral sphincter complex or the PFMs during sustained detrusor contraction [540]. The exact causes of this lack of relaxation, or contraction, are often elusive but might be due to sympathetic hyperactivity or hypertrophy of the bladder neck smooth muscle for primary bladder neck obstruction [541], or may be mostly behavioural for dysfunctional voiding [542].

4.5.2.3 Aetiology

Conditions associated with anatomical BOO include POP, incontinence surgery, urethral stricture, urethral stenosis, urethral diverticulum, urethral caruncle, urethral malignancies and paraurethral masses.

Conditions associated with functional BOO include primary bladder neck obstruction, dysfunctional voiding, and idiopathic urinary retention (Fowler's syndrome).

In primary bladder neck obstruction, the bladder neck fails to open adequately during voiding, in the absence of an anatomical obstruction [543]. It is estimated that 4.6–16% of women presenting with voiding symptoms have primary bladder neck obstruction [541].

Dysfunctional voiding is due to involuntary intermittent contractions of the periurethral striated or levator muscles during voiding in neurologically normal women, and is thought to be caused by faulty learned toileting behaviour [495]. There is also some evidence of a link between dysfunctional voiding and a history of sexual abuse [544].

Idiopathic urinary retention, also known as Fowler's syndrome, is a primary disorder of the external urethral sphincter with hypertrophy of the muscle fibres, which fail to relax during micturition. It is associated with decreased detrusor contractility via enhancement of the guarding reflex. It is seen most often, but not exclusively, in young women with urinary retention and is characterised by increased urinary sphincter volume and activity/tone, which may be hormonally triggered [545].

Alpha-adrenergic agonists, such as pseudoephedrine commonly contained in decongestants, can lead to some form of functional obstruction due to their stimulatory effects, which may contract the bladder neck and lead to urinary retention [546].

Neurological conditions can also bring about functional BOO in women. These conditions are not considered in these guidelines and are covered elsewhere [9].

*4.5.3 **Classification***

4.5.3.1 Anatomic bladder outlet obstruction

Anatomical BOO involves a physical or mechanical obstruction of the outflow of urine.

4.5.3.2 Functional bladder outlet obstruction

Functional BOO involves a non-anatomical, non-neurogenic obstruction of the outflow of urine resulting from non-relaxation or increased tone in the bladder neck and/or urethral sphincter complex or the PFMs (Table 5). Neurological causes of functional BOO are not considered in these guidelines and are covered elsewhere [9].

Table 5: Main causes of female bladder outlet obstruction

Functional BOO	Anatomical BOO
• Primary bladder neck obstruction • Dysfunctional voiding • Idiopathic urinary retention (Fowler's syndrome)	• Urethral stricture • Anti-incontinence surgery • Pelvic organ prolapse • Urethral diverticulum • Urethral caruncle • Urethral malignancies • Paraurethral masses

4.5.3.3 Recommendation for classification of bladder outlet obstruction

Recommendation	Strength rating
Use standardised classification of bladder outlet obstruction in women (anatomical or functional), and research populations should be fully characterised using such classification.	Strong

*4.5.4 **Diagnostic evaluation***

Diagnosis of BOO in women, although dependent on formal pressure–flow studies, may be suggested by several clinical and other non-invasive assessments.

4.5.4.1 Clinical history

In terms of clinical history, a range of LUTS may be elicited and these may not be confined to voiding LUTS. Women may not present until they have the possible complications of BOO, such as recurrent UTI, chronic urinary retention or acute/chronic kidney disease [535]. The evidence regarding clinical utility of symptoms for the diagnosis of BOO is inconclusive. In a single-centre retrospective study involving 587 women, 38 of whom were diagnosed with BOO, the authors concluded that symptom assessment alone was insufficient for diagnosis and a full urodynamic evaluation was essential [547]. A smaller retrospective study of 57 premenopausal women with bothersome LUTS found a significantly higher proportion of women with bladder dysfunction presenting with UUI. Patients with voiding phase dysfunction have higher total scores and voiding symptom subscores in the American Urological Association (AUA) symptom index [548]. Perhaps some of the difficulty in evaluating the diagnostic accuracy of urinary symptoms comes from the observation that a significant proportion of women presenting with obstruction also have concomitant urodynamic abnormalities. In a large study of > 5000 women with urinary symptoms including 163 with BOO, additional urodynamic diagnoses were noted in 54% [549]. Similarly, in a study involving 101 women with a primary diagnosis of SUI, the prevalence of BOO (based on maximum urine flow [Q_{max}] < 12 mL/s and maximum detrusor pressure at Q_{max} > 25 cm H_2O) was 16% [550]. Symptoms alone were not sufficient to discriminate between the various different diagnostic groups of women in these two studies. LUTS appear to be fairly sensitive to change following intervention for BOO. A prospective study in 53 women with clinically suspected voiding dysfunction describes significant symptom improvement in twelve of sixteen patients who underwent surgical intervention [551].

4.5.4.2 Clinical examination

There are no studies evaluating the clinical utility of physical examination in women with suspected BOO; nevertheless, it is widely considered as a key part of the medical assessment. It allows for visual inspection of the urethra and vagina for possible causes of mechanical obstruction as well as an assessment of the pelvic floor, which may be the cause of functional obstruction.

4.5.4.3 Uroflowmetry and post-void residual volume

Reduced Q_{max} and incomplete bladder emptying can result from weakness in the contractile strength of the detrusor muscle, or increased outlet resistance due to functional or anatomical/mechanical BOO. The use of uroflowmetry to differentiate between anatomical and functional BOO was explored in a retrospective study of 157 women [542], which concluded that Q_{max} was significantly lower in patients with anatomical obstruction, but a large degree of overlap was noted. The largest evaluation of the diagnostic utility of urine flow studies and PVR volume estimation was a retrospective analysis of > 1900 patients with symptoms of voiding dysfunction, of whom, > 800 were diagnosed with BOO based on urodynamic assessment [552]. Functional BOO was > 6 times more common than anatomical/mechanical obstruction, which does not agree with most of the other epidemiological literature for female BOO. The authors found that although urine flow rate alone was

not accurate enough to diagnose BOO, PVR of ≥ 200 mL could differentiate bladder neck dysfunction from the other causes of BOO, with a receiver-operator characteristics (ROC) area under the curve (AUC) of 0.69. Conversely, in a retrospective study involving 101 women primarily presenting with SUI, a good correlation between abnormal uroflowmetry and urodynamic obstruction (phi = 0.718, $p < 0.0001$) was found [550]. In a prospective study of > 50 women with a clinical diagnosis of voiding dysfunction, abnormal uroflow curves were observed in ~40% of women, but BOO based on pressure–flow results was confirmed in only 52% of these women [551].

4.5.4.4 Ultrasound

The major utility of US scanning in women with BOO is to detect possible complications such as bladder wall thickening or upper tract dilatation/hydronephrosis. However, the diagnostic capabilities of US have been investigated in a prospective case–control study of 27 patients with cystoscopically confirmed bladder neck obstruction [553]. The diagnostic value of shear wave elastography (SWE) and acoustic radiation force impulse imaging (ARFI) for female BOO was compared and the authors concluded that ARFI was more accurate than SWE, but a combination of the techniques was superior to both alone. Ultrasound scanning was further evaluated in a small study of fifteen women with BOO diagnosed urodynamically [554]. The authors proposed that transvaginal ultrasonography was able to demonstrate a closed bladder neck during attempts at micturition and concluded that this modality was useful for evaluation of the possible causal factors of female BOO, such as primary bladder neck obstruction.

4.5.4.5 Magnetic resonance imaging

The role of MRI in the diagnostic evaluation of female patients with suspected BOO is poorly defined. Although MRI allows for precise anatomical evaluation of pelvic structures, there are no reports of its clinical utility in the diagnosis of female BOO. Magnetic resonance imaging in patients with pathological urethral stricture can determine the degree of periurethral fibrosis, although the prognostic and clinical significance of such a finding has not been established [555].

4.5.4.6 Electromyography

Electromyography (EMG) has been most extensively studied in the subgroup of women with BOO due to idiopathic urinary retention caused by a high-tone non-relaxing sphincter (Fowler's syndrome). Abnormal urethral EMG activity may be associated with non-relaxation of the striated sphincter, abnormally high urethral pressure, and, through an exaggerated guarding reflex, poor bladder sensation and reduced detrusor contractile strength [544, 556]. Complex repetitive discharges and decelerating bursts are specific urethral EMG abnormalities that have been described in patients with high-tone non-relaxing sphincter, although these abnormalities have also been noted in asymptomatic volunteers [557, 558]. A review of voiding dysfunction in women included 65 studies with only a small number addressing the diagnostic utility of PFM EMG [495]. The authors commented that increased EMG activity of the PFM can be seen during voiding or non-relaxation, and when this is coupled with pressure–flow information from urodynamics, it may be useful to differentiate between functional and anatomical obstruction. Further evidence for this comes from a retrospective study of 157 women with roughly equal numbers of women with functional and anatomical obstruction, which concluded that a low level of PFM EMG activity is characteristic of anatomical obstruction [542]. Additional neurophysiological tests, such as anal sphincter EMG, bulbocavernosus reflex, and pudendal sensory evoked potentials can assess the integrity of the somatic S2–4 nerve roots; however, their clinical utility in the context of non-neurogenic female BOO needs to be better defined [544].

4.5.4.7 Cystourethroscopy

Cystourethroscopy can be useful to visualise any anatomical/mechanical obstruction and provide information regarding its nature, location and calibre. Given that pelvic malignancy may cause anatomical BOO, cystourethroscopy is considered an essential part of the diagnostic pathway. Formal urethral calibration may be useful for women with BOO secondary to pathological urethral stricture and various different urethral calibre thresholds have been used, from 14 to 20 Fr [559].

4.5.4.8 Urodynamics and video-urodynamics

Pressure–flow studies are the mainstay of BOO diagnosis and the characteristic abnormalities are a combination of low flow and concomitant high detrusor pressure [543]. However, while the general definition of BOO is well established, with some data supporting its clinical validity in male patients [560], the urodynamic definition of female BOO remains controversial [540]. Several urodynamic criteria have been introduced during the past twenty years but none has been established as a standard due to lack of clinical validation [540, 561]. The Blaivas and Groutz nomogram, which plots free Q_{max} and maximum detrusor pressure ($P_{det.max}$) measured during urodynamic studies, is one of the most popular [562] but has been suggested to overestimate

obstruction [563]. The addition of fluoroscopic imaging suggested by Nitti and colleagues introduces a video-urodynamic criterion for obstruction and has found popularity [77]. However, both methods lack data supporting their clinical validity, especially regarding their predictive value for therapeutic intervention outcomes [75].

In a large retrospective study of 1914 patients, 810 of whom were diagnosed with BOO, several urodynamic cut-off values were determined by ROC curve analysis to optimise the diagnostic accuracy of video-urodynamic studies [552]:

- $P_{det}Q_{max} \geq 30$ cm H_2O for differentiating BOO from bladder dysfunction and normal studies (ROC AUC = 0.78);
- the Abrams-Griffiths number > 30 for differentiating anatomical from functional BOO (ROC AUC = 0.66);
- $P_{det}Q_{max} \geq 30$ cm H_2O for differentiating dysfunctional voiding from poor relaxation of the external sphincter (ROC AUC = 0.93).

Other smaller studies with a similar methodology of utilising ROC curve analysis have concluded that neither pressure–flow data only, nor clinical symptoms alone, may be sufficient for diagnosing obstruction in women [564], therefore independent validation of any suggested thresholds is necessary.

More recently, Solomon and Greenwell devised a female BOO nomogram that parallels the ICS nomogram used for male BOO [565]. It allows the calculation of an alternative BOO female index (BOOIf), using a formula closely aligned to its male counterpart: $BOOIf = P_{det}Q_{max}\text{-}2.2Q_{max}$.

It is interpreted with a different algorithm however:

- BOOIf < 0: < 10% probability of obstruction;
- 5 < BOOIf < 18: equivocal, ≥ 50% likelihood of obstruction;
- BOOIf > 18: 90% likelihood of obstruction.

The Solomon–Greenwell nomogram was the first to be tested for clinical validity. In a recent series of 21 unselected consecutive women treated for BOO, the authors observed significant improvement of all urodynamic parameters (Q_{max}, $P_{det}Q_{max}$ and BOOIf) in female patients who became asymptomatic postoperatively [566].

An alternative urodynamic parameter of area under the detrusor pressure curve during voiding (corrected for voided volume) has been proposed following a prospective study of 103 women [567]. The authors concluded that this variable appears to be the most discriminating urodynamic parameter for the diagnosis of female BOO. This suggested diagnostic method has not been independently validated.

Voiding cystourethrography (VCUG) alone or in conjunction with concomitant pressure–flow studies may be useful in delineating the site of obstruction. Characteristic features include:

- radiographic evidence of obstruction between the bladder neck and distal urethra in the presence of
- sustained detrusor contraction [77];
- lack of funnelling appearance of the bladder neck/tight bladder neck in primary bladder neck obstruction;
- proximal dilatation of the urethra with distal narrowing in women with urethral stricture disease or pelvic-floor hypertonicity.

It is not uncommon for women with a voiding dysfunction, specifically functional BOO, to be unable to provide a flow during (video)urodynamic testing. Failure to relax the PFM can enhance the guarding reflex, limiting detrusor contractility.

4.5.4.9 Summary of evidence and recommendations for diagnosis of bladder outlet obstruction

Summary of evidence	**LE**
Evaluation of LUTS by history and examination alone is insufficient to accurately diagnose female BOO.	3
Urine flow studies cannot diagnose with high accuracy BOO in women.	3
Ultrasound scanning is unable to diagnose with high accuracy BOO in women.	2b
Electromyography alone is unable to diagnose with high accuracy BOO in women, although it may be of use in combination with pressure–flow studies and in differentiation of anatomical and functional BOO.	3
Urodynamics (often combined with video-fluoroscopy) is the standard test for evaluating female BOO.	3

Recommendations	Strength rating
Take a full clinical history and perform a thorough clinical examination in women with suspected bladder outlet obstruction (BOO).	Strong
Do not rely on measurements from urine flow studies alone to diagnose female BOO.	Strong
Perform cysto-urethroscopy in women with suspected anatomical BOO.	Strong
Perform urodynamic evaluation in women with suspected BOO.	Strong

*4.5.5 **Disease management***

Therapeutic interventions for BOO aim to decrease outlet resistance in order to increase urinary flow, improve bladder emptying and thus reduce voiding and storage LUTS [75, 540, 561]. Treatment choice is commonly dictated by the nature of the underlying cause of the obstruction.

4.5.5.1 Conservative management

4.5.5.1.1 Behavioural modification

Behavioural modification aims to improve or correct maladaptive voiding patterns through analysis and alteration of the relationship between the patients' symptoms and their environment, lifestyle and habits. Behavioural modification interventions are often tailored to individual patients' needs, symptoms and circumstances and can include elements such as education regarding normal voiding function, self-monitoring of symptoms, changes in lifestyle factors that may affect symptoms, avoidance of constipation, and alteration of voiding technique. Ultimately, techniques aim to improve the coordination between the detrusor and sphincter, resulting in their synergistic action [75, 540, 561].

The vast majority of individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. General interventions such as those listed above may help with symptoms resulting from BOO but no quantification of their effect is possible.

4.5.5.1.2 Pelvic floor muscle training +/- biofeedback

Pelvic floor muscle training aims to improve pelvic floor function and urethral stability. In the context of BOO, physiotherapy aims to teach patients to relax their PFMs and striated urethral sphincter during voiding. Pelvic floor muscle contraction, particularly in women with pelvic floor dysfunction, has been shown to significantly reduce vaginal resting pressure and surface EMG activity [514]. A twelve-week PFMT programme in postmenopausal women demonstrated significant improvement in the speed of relaxation after PFM contraction and a decrease in PFM tone [515].

As mentioned in the section discussing UAB (Section 4.4.4.1.2), most of the evidence supporting PFMT in dysfunctional voiding is from paediatric studies.

A case-series reported improved PFM relaxation and voiding function following PFMT with biofeedback in fifteen women with dysfunctional voiding based on a dilated proximal urethra on voiding cysto-urethrography and hyperactivity of the pelvic muscles or external urethral sphincter on EMG during voiding. No clinical outcomes were reported by this series [568].

4.5.5.1.3 Electrical stimulation

Application of electrodes that allow for controlled contraction and relaxation of the PFMs may theoretically facilitate the relaxation of the external sphincter and pelvic floor but no critical evaluation of this intervention in women with BOO has been published.

4.5.5.1.4 Use of vaginal pessary

Intravaginal devices such as pessaries aim to relieve voiding symptoms and improve bladder emptying by physical correction of the obstruction caused by a POP. In a prospective study of eighteen women with grade three or four cystocoeles and diagnosed with BOO by urodynamics (defined as $P_{det}Q_{max}$ > 25 cm H_2O, Q_{max} < 15 mL/s), normal voiding was noted in seventeen (94%) immediately after placement of a vaginal pessary. No other outcomes were available in this series [569]. No long-term data are available on the use of vaginal pessary for BOO.

4.5.5.1.5 Urinary containment

Urinary containment devices include body-worn absorbent products. Their use in BOO is to achieve social continence in patients with urinary retention and associated overflow UI and they are often only a temporary measure. There are no published studies on the outcomes or adverse events associated with the use of urinary containment devices for the management of female BOO. While there may be no studies exclusively involving women with BOO, there are many involving women with UI who may have BOO as an underlying cause.

4.5.5.1.6 Urinary catheterisation

Significant urinary retention from BOO may be addressed by actively bypassing the obstruction and draining the residual urine. Catheterisation may be used as a treatment itself or as an adjunct to an initial treatment of urethral dilatation or urethrotomy or bladder neck incision. There are two ways of using a catheter: CISC or indwelling catheterisation [116].

After UI surgery, BOO may be managed by short-term catheterisation in most patients who have transient postoperative voiding difficulty. For a few women who develop chronic urinary retention, CISC or indwelling catheterisation may be offered [495].

A small RCT investigated the effectiveness of CISC to prevent recurrence after internal optical urethrotomy for urethral stricture disease. In the treatment group, CISC was done twice a day for one week, and once a day for four weeks, then once weekly for seven weeks post-urethrotomy. Freedom from stricture recurrence, determined by urethrography and uroflowmetry performed twelve weeks postoperatively, was higher in the catheterisation group compared to the group with no catheterisation (78.5% vs. 55.4%) [570]. This finding mirrors the Cochrane review on self-dilatation for urethral stricture among men that showed less recurrence with the performance of self-dilatation [571].

In a series of 20 patients with voiding dysfunction after TVT who were put on a CISC programme, overall cure rate was 59%, with cure defined as consistent residual volume < 100 mL. Half of these patients were voiding normally within twelve weeks [572].

A patient satisfaction survey involving 188 patients on CISC/self-dilatation, which included 38 patients with urethral stricture, showed positive (pleased or satisfied) outcomes in 54.3% of patients, while 28.2% had mixed feelings and 9.6% were unhappy. No rates were given specifically for the BOO group [573].

4.5.5.1.7 Intraurethral inserts

An intraurethral insert is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. The valve-pump mechanism is operated by an external control unit, which activates to open the valve and the pump to draw urine from the bladder and allow voiding. At the end of urination, the pump ceases to rotate and the valve closes to regain continence. The insert is routinely replaced once a month.

Only one study reported the use of this device in 92 women with voiding dysfunction of various aetiologies including multiple sclerosis, prior pelvic surgery, pelvic radiation, diabetes mellitus, and spinal stenosis and injury. The device was removed within seven days of insertion in 60% of the cases due to discomfort, pericatheter leakage or technical difficulty. An additional 20% of patients had late discontinuation. All those who continued to use the device were satisfied, with PVR volumes remaining < 100 mL. Adverse events included migration into the bladder in six cases and symptomatic UTI in four cases [574, 575]. Extended, long-term data on the use of urethral inserts are not available.

4.5.5.1.8 Extracorporeal magnetic stimulation

Extracorporeal magnetic stimulation involves the patient sitting on a device that induces consistent PFM contraction and relaxation by repeated magnetic stimulation of motor nerve fibres. Extracorporeal magnetic stimulation contracts and then relaxes the PFM following a set frequency and interval. It is postulated that patients could therefore learn to spontaneously contract or relax the PFM, which may enhance their ability to relax their pelvic floor while voiding [576].

In a small (n = 60) prospective non-randomised trial, alfuzosin was compared to EMS and to the combination of alfuzosin + EMS in women with functional BOO. They observed significant increase of Q_{max} and significant decrease of International Prostate Symptom Score (IPSS) in all groups and significantly greater improvement in the QoL question of the IPSS in the combination therapy group [576].

4.5.5.1.9 Summary of evidence and recommendations for conservative treatment of bladder outlet obstruction

Summary of evidence	**LE**
Pelvic floor muscle relaxation training with biofeedback may result in relaxation of the pelvic muscles and external urethra in women with dysfunctional voiding.	3
There is no available evidence in the published literature on the clinical effect of ES for management of female BOO.	NA

In women with large (grade three or four) cystocoeles causing bladder outlet obstruction (BOO), placement of a vaginal pessary may improve voiding efficiency.	3
Regular CISC after urethrotomy is better than no catheterisation to prevent recurrence of urethral strictures.	1b
A CISC programme in women with voiding dysfunction after TVT has a cure rate of 59%.	3
Women who use an intraurethral device have lower PVR volume but most require its removal due to complications.	3
Extracorporeal magnetic stimulation combined with alfuzosin may be more effective than either of these therapies alone in women with functional BOO.	2a

Recommendations	Strength rating
Offer pelvic floor muscle training (PFMT) aimed at pelvic floor muscle relaxation to women with functional bladder outlet obstruction (BOO).	Weak
Prioritise research that investigates and advances understanding of the mechanisms and impact of PFMT on the coordinated relaxation of the pelvic floor during voiding.	Strong
Offer the use of a vaginal pessary to women with grade three or four cystocoeles and BOO who are not eligible/inclined towards other treatment options.	Weak
Offer urinary containment devices to women with BOO to address urinary leakage as a result of BOO, but not as a treatment to correct the condition.	Weak
Offer clean intermittent self-catheterisation to women with urethral strictures or post-urinary incontinence surgery for BOO.	Weak
Do not offer an intraurethral device to women with BOO.	Strong

*4.5.6 **Pharmacological management***

4.5.6.1 Alpha-adrenergic blockers

Alpha-adrenergic blockers are postulated to relieve LUTS caused by BOO in women via smooth muscle relaxation in the bladder neck, thus decreasing bladder outlet resistance [577].

Systematic reviews on the use of alpha-blockers in women generally involve studies with a population that includes women complaining of LUTS and voiding dysfunction. Confirmation of BOO is often not required in the trials included [578, 579]. These reviews showed significant improvements in symptoms and urodynamic parameters associated with their use [578-580]. A meta-analysis of fourteen RCTs comparing alpha-blockers and placebo in women with LUTS showed significant symptom relief after alpha-blocker treatment relative to placebo, but no significant difference in Q_{max}, PVR and adverse event rates [578]. This is in contrast to prospective non-comparative trials that consistently showed improvements in voiding and storage symptoms, bother scores, and urodynamic parameters [Q_{max}, PVR, $P_{det}Q_{max}$, MUCP after alpha-blocker use compared to baseline [521, 522, 581-583].

A SR performed by the Panel of studies on alpha-blockers used specifically for women with BOO included one placebo-controlled RCT, one RCT comparing two types of alpha-blockers, and six prospective non-comparative studies. In the only placebo-controlled RCT reporting subgroup analyses in women with urodynamically proven BOO (based on the Bladder and Groutz nomogram) no significant difference was observed in the changes of IPSS, IPSS sub scores, Q_{max}, PVR volume and bladder diary after eight weeks of alfuzosin (n = 58) vs. placebo (n = 59). Of note, no EMG and/or voiding cysto-urethrography was used to distinguish between dysfunctional voiding and primary bladder neck obstruction [584].

Information on the comparative effectiveness of the different types of alpha-blockers was limited to one RCT. A small trial of 37 women with IPSS > 8, Q_{max} < 12 mL/s and PVR volume > 50 mL, compared tamsulosin and prazosin over a three-month treatment period. More patients treated with tamsulosin were completely satisfied with their treatment (16/20 vs. 9/20). Both treatment groups showed significant improvement in symptom scores from baseline but no further statistical comparison between the groups was done. However, a larger decrease in the AUA Symptom Index was seen in the tamsulosin group compared with the prazosin group. More adverse events were reported with prazosin (thirteen vs. one case) [585].

A small three-arm non-RCT in women with functional BOO compared alfuzosin monotherapy and EMS. The combination of alfuzosin and EMS showed greater improvement in storage symptoms and QoL than alfuzosin monotherapy alone [576].

4.5.6.2 Striated muscle relaxants

Baclofen is a gamma-aminobutyric acid (GABA) agonist that exerts its effect on the GABAergic interneurons in

the sacral inter-mediolateral cell column responsible for the relaxation of the striated urinary sphincter during voiding. Intrathecal administration has been shown to improve voiding in a trial among patients with spinal cord injury. Oral baclofen has also been widely studied [561].

A randomised placebo-controlled crossover trial investigated the efficacy and safety of a four-week course of oral baclofen 10 mg three times/day in 60 women diagnosed with BOO, based on increased EMG activity with sustained detrusor contraction during voiding. It showed a lower number of voids, significant improvements in Q_{max} and $P_{det}Q_{max}$ with baclofen compared with placebo. Post-void residual volume, maximum cystometric capacity and MUCP were not significantly different between the groups. Adverse event rates were also similar, with the most common being somnolence, dizziness and nausea. An important limitation of this study was the lack of patient-reported outcomes to assess symptoms and QoL [586].

A small case series reported the outcomes of 20 women with functional BOO who were given oral baclofen 5 mg three times/day for twelve weeks. There was significant improvement in the mean voided volume and BVE. However, Q_{max}, $P_{det}Q_{max}$, PVR volume and urethral profile pressures did not significantly change. No significant adverse events were noted [587].

4.5.6.3 Oestrogens

The relative reduction in urethral wall compliance seen in atrophic urethritis due to oestrogen deprivation may be responsible for urethral obstruction in postmenopausal women. Oestrogen therapy is thus theoretically expected to improve the condition. There are no published studies on the use of oestrogens specifically for the management of female BOO.

4.5.6.4 Sildenafil

Sildenafil, by inhibiting phosphodiesterase 5, increases the levels of nitric oxide in the female urethral sphincter, thereby promoting urethral relaxation.

A placebo-controlled, randomised crossover trial that included twenty women with partial or complete retention or obstructive voiding, with high MUCP and elevated US-estimated sphincter volume (> 1.6 cm) showed that while there was significant improvement in symptom scores and urodynamic parameters from baseline with sildenafil treatment, this difference was not significant when compared with placebo [588].

4.5.6.5 Thyrotropin-releasing hormone

Intravenous thyrotropin-releasing hormone (TRH) has been postulated as a neurotransmitter that induces urethral relaxation [589]. The exact mechanism is unclear.

In a small RCT of sixteen women with voiding difficulty, eight (three with BOO) were randomised to receive 200 µg intravenous bolus of TRH, and eight (three with BOO) received saline. No difference in the decline in functional profile lengths and maximum urethral closure pressures were noted between treatment groups, despite a significant decline noted from baseline in the treatment group. No subgroup analysis of women with BOO was reported [589].

4.5.6.6 Summary of evidence and recommendations for pharmacological management

Summary of evidence	**LE**
Alpha-adrenergic blockers are associated with significant improvement in symptom scores from baseline, but not urodynamic parameters compared with placebo.	1a
Tamsulosin is associated with greater improvement in symptom score compared with prazosin.	1b
Non-specific alpha-blockers are associated with higher rates of adverse events.	1b
Oral baclofen is better than placebo in improving Q_{max} and $P_{det}Q_{max}$, but not other urodynamic parameters. Its effects on symptoms are not well reported.	1b
Current evidence does not show that sildenafil is superior to placebo in improving symptoms or urodynamic parameters of female patients with BOO.	1b
Trials including women with voiding problems of mixed aetiologies showed no difference in urodynamic outcomes between intravenous TRH and placebo.	1b

Recommendations	**Strength rating**
Offer uroselective alpha-blockers, as an off-label option, to women with functional bladder outlet obstruction (BOO) following discussion of the potential benefits and adverse events.	Weak

Offer oral baclofen to women with BOO, particularly those with increased electromyography activity and sustained detrusor contraction during voiding.	Weak
Only offer sildenafil to women with BOO as part of a well-regulated clinical trial.	Strong
Do not offer thyrotropin-releasing hormone to women with BOO.	Strong

*4.5.7 **Surgical management***

4.5.7.1 Intra-sphincteric botulinum toxin injection

Botulinum toxin inhibits the presynaptic release of acetylcholine, which reduces urethral sphincter tone. It is also believed to decrease the release of noradrenaline in the urethra to counteract external urethral sphincter overactivity [590].

Evidence on the use of botulinum toxin for female BOO is limited to small case series. Most studies included mixed populations without subgroup analyses, or the diagnosis of voiding dysfunction could not be ascertained as solely resulting from BOO. No comparative trial exclusively involving female BOO patients using botulinum toxin has been identified in the literature.

A SR including several reports of small case series using variable doses of botulinum toxin A injected periurethrally in women with dysfunctional voiding showed improvements in symptoms, and reductions in residual volume and voiding detrusor pressure. Larger series in adults (both sexes) showed success rates of 86–100% [590].

A double-blind, placebo-controlled RCT (n = 73) 100 U onabotulinumtoxinA vs. saline resulted in significantly lower IPSS score and larger voided volume compared with saline in 31 men and women with dysfunctional voiding. Dysfunctional voiding was defined by a spinning top appearance on real-time fluoroscopy, poorly relaxed urethral sphincter on EMG, and a normal-to-high voiding pressure with a low and/or intermittent urinary flow rate, a PVR volume > 300 mL, and a low voiding efficiency. Other urodynamic parameters were comparable between the groups [591]. A subgroup analysis on the female population of this study was not available.

Two small case series in women with BOO reported the effects of 100 U intra-sphincteric injection of BTA. Both showed improvement in symptom and bother scores and significant reduction in PVR volume [544, 592]. One study reported increased Q_{max} and improved static urethral pressure profile (UPP) [544]. The average symptom-free duration was 16.8 weeks in another study [592]. Adverse events included UTI and temporary need for CISC. No SUI was reported.

4.5.7.2 Sacral nerve stimulation

Sacral nerve stimulation is a type of neuromodulation that allows continuous ES from an electrode placed alongside the sacral nerve via a surgically implanted pulse generator. Electrical stimulation is postulated to decrease urethral tone. Sacral nerve stimulation is also postulated to work by blockade of the inhibitory urethral afferent impulses, which cause inhibition of normal bladder contraction.

No comparative trial as been identified in the literature on the use of neuromodulation for female BOO.

Most publications on neuromodulation for voiding dysfunction are retrospective reviews of cases, involving a mix of patient populations who underwent the procedure for different indications. In studies that indicated a subgroup of patients with urinary retention, there was either no urodynamic confirmation of the nature of the retention or separate outcomes were not reported for participants with retention.

A review of 60 women who underwent for urinary retention associated with outlet obstruction (defined as UPP > 100 cm H_2O, increased urethral sphincter volume > 1.8 mL, and abnormal EMG with repetitive discharges and decelerating bursts) showed an overall spontaneous voiding rate of 72% over a mean follow-up of four years. Of those who continued to require CISC up to twice daily postoperatively, the frequency was less than prior to surgery (degree not specified). There were 99 adverse events and 63 surgical revisions. In this series, half of the patients underwent a one-stage SNS procedure and the other half a two-stage procedure. The proportion of patients who required CISC-assisted voiding was higher in the two-stage group (27% vs. 17%). More serious adverse events (defined as events requiring admission or surgical revision to resolve issues such as loss of response, lead migration and surgical revisions) were associated with the one-stage procedure [588].

In a single-centre series in a subgroup of 32 patients diagnosed with idiopathic urinary retention (Fowler's syndrome) who underwent SNS, 62.5% achieved a > 50% reduction in CISC rate [593].

4.5.7.3 *Pelvic organ prolapse surgery*

Pelvic organ prolapse surgery may relieve BOO by correcting the urethral kinking caused by the prolapse or by relieving the urethral compression brought about by the prolapsing organ [75, 540, 561].

Bladder output obstruction due to POP may be addressed by corrective surgery. Based on reviews, the majority of patients who had BOO caused by POP who had repair of their cystocoele demonstrated improvement of their voiding difficulties [495, 594].

A multicentre prospective study involving 277 women with at least grade two symptomatic POP who underwent surgery demonstrated a significant reduction in voiding symptoms and PVR volume one year postoperatively [595].

A retrospective study of 50 women who underwent laparoscopic sacrocolpopexy for POP showed a significant increase in mean postoperative Q_{max} and decrease in $P_{det}Q_{max}$ and PVR in those aged ≥ 65 years. The OAB symptom score improved but there was no significant difference in the ICIQ-SF score postoperatively [596].

In a case series of 35 women with stage III or IV POP presenting with a preoperative PVR volume > 100 mL (mean 226 mL), 89% had PVR volume < 100 mL postoperatively [597]. In another case series of 39 patients with cystocoeles who complained of voiding symptoms preoperatively, 30 (79%) achieved normal voiding, defined as no obstructive symptoms and a PVR volume < 50 mL, after bladder neck suspension with anterior colporrhaphy [598].

4.5.7.4 *Urethral dilatation*

Urethral dilation involves the passage of sequentially greater diameter dilators into the urethra, causing the obstructing fibrotic tissue to break open, thereby widening the lumen. It is considered the primary procedure of choice for women suspected of urethral stricture disease [559]. Dilation of up to 30–40 Fr has been done. There is no standard dilatation technique; dilatation of up to 43 Fr has been described, although other authors suggest dilating to 30 or 35 Fr.

A SR of female urethral stricture management included three trials involving urethral dilatation. Pooled analysis of data from 93 women showed a mean success rate of 49% after urethral dilation to 41 Fr with a mean follow-up of 46 months. Mean time to failure was twelve months. In treatment-naïve patients, success rate (as defined by trialists) was 58%, compared with 27.2% in patients who had undergone previous dilatation [555].

An RCT of 50 women with OAB syndrome and associated urodynamically confirmed BOO (defined as a Q_{max} < 15 mL/s with a voided volume of ≥ 100 mL and/or PVR volume > 200 mL, not due to urethral stricture) compared the effect of cystoscopy and bladder distension with urethral dilatation (n=22) and cystoscopy only (n=28) after six weeks' follow-up. Significantly more patients who had cystoscopy only had persistent urgency at six weeks and six months postoperatively. Urodynamic parameters did not significantly change pre- and postoperatively in both groups. The greater improvement in QoL scores based on the King's Health Questionnaire domain scores seen in the non-urethral dilatation group in this trial should be interpreted cautiously because of the higher baseline scores. There were no significant changes in Q_{max}, PVR volume, voided volume or $P_{det}Q_{max}$ in any of the two groups at six weeks' questioning of the role of any of these two options for therapeutic management of BOO. Also, six patients (12%) developed postoperative SUI [599].

A prospective trial of 86 women with primary urethral stricture compared on-demand vs. intermittent urethral dilatation to 24 Fr (dilate every two months). It showed an overall increase in Q_{max} and decrease in PVR volume post-dilatation. Significantly greater improvements were seen in the intermittent urethral dilatation group [600].

Three small case series showed improvements in symptoms with relief of urgency and/or UUI but inconsistent results in terms of significant improvement in Q_{max}, PVR volume and $P_{det}Q_{max}$. Benefits were poorly sustained, with most patients requiring additional or repeat intervention in the long-term [601-603].

Worsening or new-onset SUI is a concern with urethral dilatation but it is less of a concern than after urethrotomy or surgical reconstruction. Patients have also reported frequency and urgency post-dilatation [603].

4.5.7.5 *Urethrotomy*

Urethrotomy involves incision of the urethra endoscopically or using a urethrotome. It addresses the urethral narrowing by cutting open the scar tissue which is causing the obstruction [75, 540, 561, 603].

A prospective study of ten women with urethral strictures investigated the effect of Otis urethrotomy to 40 Fr followed by six weekly dilatations. There was significant improvement in IPSS, QoL, voided volume, Q_{max} and PVR volume at six months. Only the improvements in PVR volume and QoL were maintained on long-term follow-up (mean 82 months) [601].

4.5.7.6 Bladder neck incision/resection

Transurethral bladder neck incision decreases resistance at the bladder neck by cutting open the hypertrophic bladder neck smooth muscle in patients with primary bladder neck obstruction. Transurethral incision of the bladder neck may be performed with a unilateral incision at the twelve o'clock position or with bilateral incisions at the five and seven o'clock, two and ten o'clock or three and nine o'clock positions, or four incisions at the three, six, nine and twelve o'clock positions. This may be done using a resectoscope with a Collin's knife, cold knife, or using laser energy. Some authors report additional resection of the bladder neck between the five and seven o'clock positions during the procedure.

Evidence on bladder neck incision or resection for female BOO is limited to non-comparative trials. A review of studies on bladder neck incision for the treatment of bladder neck obstruction in women reports success rates of 76–100% [543].

Bladder neck incision was compared with V-Y-reconstruction using Nesbit's technique in a retrospective study of seventeen women with BOO, diagnosed by various uroradiological, endoscopic and urodynamic investigations. The results showed similar symptomatic improvement rates and postoperative PVR volume between the two groups. V-Y plasty had a longer operating and catheter time, lower uroradiological improvement rate, higher transfusion rate, and higher adverse event rate [604].

Several prospective case series consistently reported significant improvements in IPSS, QoL, Q_{max}, $P_{det}Q_{max}$ and PVR volume after treatment compared to baseline, regardless of the site of the incision, type of energy used or the length of follow-up [605-608].

The largest case series with 84 patients diagnosed with primary bladder neck obstruction (based on lack of funnel shape of the bladder neck during voiding on voiding cysto-urethrography, $P_{det} > 20$ cm H_2O and $Q_{max} < 12$ mL/s) showed success in 84.5% of patients with improvement in IPSS, QoL, Q_{max} and $P_{det}Q_{max}$ after mean follow-up of 27.4 months (6–78 months). Complications included vesico-vaginal fistula (VVF) (3.6%), SUI (4.7%) and urethral stricture (3.6%) [605].

No comparisons have been made between the different incision techniques (location, length and depth of incision, implement used – cold knife vs. hot knife vs. laser, with or without resection). However, in a case series of 84 patients, complications of VVF and SUI were noted in the cohort of patients who had their incisions at two and ten o'clock positions, and not in those who had their incisions at two and ten o'clock [605].

Adverse events include SUI, requirement for reoperation, and recurrence. Postoperative SUI was reported in 3– 33% [543].

4.5.7.7 Urethroplasty/urethral reconstruction

Surgical reconstruction of the female urethra has been used in the management of extensive urethral stricture. Several urethroplasty techniques have been reported including the use of vaginal or labial flaps, as well as vaginal and buccal grafts after cutting open the fibrotic tissue causing the urethral obstruction [609]. The use of bladder flaps has also been reported [610], and laboratory-engineered tissue grafts have also been used [610].

The surgical approaches have been described based on the position relative to the urethra; dorsal, ventral or circumferential. The dorsal approach is believed to provide better mechanical support and a more vascularised bed for a graft or flap. However, there is greater risk of damage to the sphincter and clitoral bodies with this approach. The ventral approach is more familiar to most surgeons and requires less urethral mobilisation. However, it is reported as being more prone to urethrovaginal fistulae, although it is not clear to what extent [559].

Reviews of studies reporting outcomes of urethroplasty state success rates of 57–100% [611]. Pooled analysis from six studies using vaginal or labial flaps showed a mean success rate of 91% with a mean follow-up of 32 months. Vaginal or labial graft urethroplasty was reported to have an 80% success rate with a mean follow-up of 22 months.

Oral mucosal grafts, reported in seven studies, had a mean success of 94% after a mean follow-up of fifteen months [559]. A later review of studies on dorsal buccal mucosal graft reported success rates of 62–100%, with a pooled success rate of 86% [612]. A long-term study with a mean follow-up of 32 months showed a stricture recurrence rate of 23.1% [611].

A retrospective comparative study of ten women who underwent urethral dilatation and twelve who underwent dorsal onlay pedicled labial flap urethroplasty, reported significant improvements in both groups in QoL, AUA Symptom Index, PVR volume and Q_{max}. The urethroplasty group had significantly better QoL scores and Q_{max} (17.0 vs. 12) at follow-up compared with the dilatation group [613]. Adverse events associated with urethroplasty include new-onset SUI and urgency and worsening of UUI.

4.5.7.8 Urethrolysis

Bladder outlet obstruction in women occurring as a complication of surgery for SUI may be managed surgically by urethrolysis, to regain urethral mobility. Urethrolysis may involve removal of periurethral anti-incontinence sutures, scar tissue and fibrosis.

Case series showed success rates measured as improved voiding and lower residual volumes, improvement or resolution of symptoms and QoL, and improvement of urodynamic parameters after treatment [614-616]. *De novo* SUI was reported in 39% in one study [616].

A study on 21 patients who underwent urethrolysis suggested an association of persistent postoperative bladder symptoms with greater delay in performing urethrolysis. Patients who presented with postoperative storage and voiding symptoms after a mean seventeen months' follow-up had a longer time to urethrolysis compared to those who had no complaints (31 vs. nine months) [617].

4.5.7.9 Removal/excision/section/loosening of mid-urethral sling

In women who develop BOO after placement of a mid-urethral sling, surgical management may include tape loosening, incision or division, and excision and/or removal of the tape [495].

Several small retrospective reviews of cases using different techniques of sling revision (incision, partial excision, or excision) showed good success rates in terms of symptom reduction, resumption of voiding with significant reduction in PVR volume and improvement of urodynamic parameters. Stress urinary incontinence recurs in a small proportion of patients and often to a lesser degree than prior to the sling procedure. Studies have shown long-term efficacy, including preservation of continence.

In a series of 63 women who presented with voiding dysfunction and persistent PVR volume > 100 mL after tape surgery for UI, different techniques were compared. Comparisons involved sling revision: sling division (n = 46) vs. partial sling excision (n = 13) vs. sling revision (division or excision) with an additional anti-SUI procedure (n = 4). The authors reported an overall success rate of 87% (PVR volume < 150 mL). No significant difference in success rates was demonstrated among the different revision techniques. There was a greater need for surgery for recurrent SUI in the partial sling excision group without an anti-SUI procedure (23% vs. 2.2 and 0) [618].

4.5.7.9.1 Timing of sling revision

One study showed that patients who underwent surgical release > 180 days after initial anti-UI surgery had significantly less recurrent SUI compared with patients who underwent the release sooner (15% vs. 46%) [619].

4.5.7.10 Summary of evidence and recommendations for surgical management of bladder outlet obstruction

Summary of evidence	**LE**
Intrasphincteric injection of botulinum toxin results in the improvement of symptoms and urodynamic parameters.	2
Sacral nerve stimulation results in spontaneous voiding and a reduction in CISC rate in the majority of female BOO patients in idiopathic urinary retention.	3
More serious adverse events and surgical revisions were associated with the one-stage neuromodulator implantation procedure.	3
Repair of POP improved PVR and voiding symptoms.	3
Urethral dilatation in women with BOO results in significant improvement in OAB symptoms, but improvements in urodynamic parameters of voiding are inconsistent.	1b

Programmed intermittent urethral dilatation results in better outcomes compared with on-demand dilatation.	3
Effects of urethral dilation are poorly sustained, requiring repeat intervention in the long term.	3
Internal urethrotomy followed by regular dilatations resulted in significant improvement in symptoms and urodynamic parameters in women with BOO.	3
Bladder neck incision in females with BOO results in improvements in symptoms and urodynamic parameters.	3
Complications of bladder neck incision are not common, but include VVF, SUI, and urethral stricture.	3
Urethroplasty using grafts or flaps in women with BOO due to urethral stricture have good success rates with significant improvements of symptoms, QoL scores and urodynamic parameters compared to baseline.	3
Urethroplasty results in better QoL and Q_{max} compared to urethral dilatation.	2
Long-term results showed significant stricture recurrence rate after urethroplasty.	3
Urethrolysis performed on women with voiding problems after anti-UI surgery resulted in improvements in symptoms, QoL and urodynamic parameters post-operatively.	3
Delayed urethrolysis was associated with persistent post-operative bladder symptoms.	3
Sling revision in women who presented with urinary retention or voiding problems and significant PVRs after sling surgery for UI resulted in improvements in symptoms and urodynamic parameters, resumption of voiding and reductions in PVRs.	3
Sling revision is associated with the risk of recurrent SUI.	3

Recommendations	**Strength rating**
Offer intra-sphincteric injection of botulinum toxin to women with functional bladder outlet obstruction (BOO).	Weak
Offer sacral neuromodulation to women with functional BOO.	Weak
Advise women with voiding symptoms associated with pelvic organ prolapse that symptoms may improve after surgery.	Weak
Offer urethral dilatation to women with urethral stenosis causing BOO, but advise on the likely need for repeated intervention.	Weak
Offer internal urethrotomy with postoperative urethral self-dilatation to women with BOO due to urethral stricture disease but advise on its limited long-term improvement and the risk of postoperative urinary incontinence (UI).	Weak
Do not offer urethral dilatation or urethrotomy as a treatment for BOO to women who have previously undergone mid-urethral synthetic tape insertion due to the theoretical risk of causing urethral mesh extrusion.	Weak
Inform women of limited long-term improvement (only in terms of post-void residual volume and quality of life) after internal urethrotomy.	Weak
Offer bladder neck incision to women with BOO secondary to primary bladder neck obstruction.	Weak
Advise women who undergo bladder neck incision on the small risk of developing stress urinary incontinence (SUI), vesico-vaginal fistula or urethral stricture postoperatively.	Strong
Offer urethroplasty to women with BOO due to recurrent urethral stricture after failed primary treatment.	Weak
Caution women on the possible recurrence of strictures on long-term follow-up after urethroplasty.	Weak
Offer urethrolysis to women who have voiding difficulties after anti-UI surgery.	Weak
Offer sling revision (release, incision, partial excision, or excision) to women who develop urinary retention or significant voiding difficulty after tape surgery for UI.	Strong
Caution women about the risk for recurrent SUI and the need for a repeat/concurrent anti-UI surgery after sling revision.	Strong

*4.5.8 **Follow up***

Women with BOO should be followed up and monitored regularly due to the risk of further deterioration of voiding or renal function in case of persistence and progression of the obstruction. For those who received treatment, monitoring must be done for recurrence of BOO. In particular, women who undergo urethral dilation, urethrotomy or urethroplasty for urethral stricture need to be monitored for stricture recurrence.

4.6 Nocturia

Nocturia was defined by the ICS in 2002 as *"the complaint that the individual has to wake at night one or more times to void"* and quantified in an updated document in 2019 as *"the number of times an individual passes urine during their main sleep period, from the time they have fallen asleep up to the intention to rise from that period"* [620]. The EAU Guidelines Panel on Urinary Incontinence conducted a SR on nocturia in women (596). The search covered evidence up to 2017 and this review was updated with a scoping search in 2020.

*4.6.1 **Epidemiology, aetiology, pathophysiology***

The prevalence of nocturia varies according to age with 4–18% of women aged 20–40 years experiencing ≥ 2 episodes per night, compared to 28–62% of women aged ≥ 70 years [621]. In a study of 1000 community-dwelling older adults, female nocturia was associated with older age, African–American race, history of UI, lower limb oedema and hypertension [622]. A report on > 5000 adults aged 30–79 years identified around 28% with nocturia and found additional correlates with increased BMI, cardiac disease, type 2 diabetes and diuretic use [623]. A SR and meta-analysis with moderate certainity evidence based on the GRADE approach, demonstrated that the higher incidence of nocturia among hyptertensive patients was more strongly associated (1.2 to 1.3 fold) among Black and Asian women, unrelated to their age or BMI status [624]. Another SR with moderate certainty of evidence based on the GRADE approach showed that nocturia was associated with a 1.2-fold increase risk of falls and possibly an approximately 1.3-fold increased risk of fractures [625]. Another SR and meta-analysis concluded that nocturia is probably associated with an ~1.3-fold increased risk of death [600].

The aetiology of nocturia is multifactorial and can include both urological and non-urological causes. Urological conditions which may exhibit nocturia as a significant symptom include OAB syndrome, BOO, DU and dysfunctional voiding. Non-urological causes include 24-hour polyuria (which includes nocturnal polyuria), congestive heart failure, sleep apnoea, restless leg syndrome, peripheral vascular disease, sleep disorders, night-time food ingestion, dependent oedema, and excessive fluid intake [626]. Given the varied aetiology of this symptom, there are a range of possible pathophysiological mechanisms, including: (1) 24-hour polyuria (e.g., diabetes mellitus, primary polydipsia, and diabetes insipidus); (2) nocturnal polyuria (e.g., behavioural, peripheral oedema, obstructive sleep apnoea, glycosuria, hormonal abnormalities and cardiac dysfunction); (3) diminished bladder capacity (e.g., OAB syndrome/detrusor overactivity, PFM dysfunction, BOO, pharmaceuticals, LUT calculi or tumours, and neurological bladder dysfunction); and (4) primary or secondary sleep disorders [627].

In postmenopausal women the relative deficiency in endogenous estrogen production is thought to exacerbate all major pathophysiological mechanisms that may underlie nocturia [628].

*4.6.2 **Classification***

Classification of nocturia is dependent on bladder diary analysis and several parameters have been defined as important [629]:

- nocturnal urine volume – total volume of urine passed during the night (this includes the first morning void but does not include the last void prior to sleep);
- maximum voided volume – largest single voided volume in 24 hours;
- nocturia index – nocturnal urine volume divided by maximum voided volume;
- nocturnal polyuria index – nocturnal urine volume divided by 24-hour urine volume;
- nocturnal urine production – nocturnal urine volume divided by duration of sleep in hours.

Analysis of these parameters allows clinical classification of nocturia based on physiological abnormalities that can cause nocturia:

- 24-hour polyuria;
- nocturnal polyuria;
- diminished bladder capacity;
- sleep disorders.

*4.6.3 **Diagnostic evaluation***

Evaluation of nocturia should include a thorough medical history and physical examination with particular reference to history of sleep disorders, fluid balance, associated LUTS, cardiovascular and endocrine comorbidity, renal disease, current medications and history of urological disease [629]. There are several nocturia-specific symptom scores, such as the ICI Questionnaire-Nocturia, Nocturia Quality of Life Questionnaire (N-QoL) and Nocturia Impact Diary; some of which were developed in men. A further screening

tool that aims to identify causes of nocturia is the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO) assessment tool [630-632].

A bladder diary is a vital initial investigation tool in patients complaining of nocturia and further supplementary investigations are guided by any abnormalities identified. Bladder diary analysis can allow for calculation of the parameters detailed in Section 4.6.2. A low nocturnal bladder capacity or global bladder capacity will be highlighted by reduced voided volumes during nocturnal hours or both night and day. This suggests an underlying urological condition such as OAB syndrome, BOO or DU. The term 24-hour polyuria is defined as 24-hour urine production > 40 mL/kg [633] and may be present in conditions such as diabetes mellitus or diabetes insipidus. The definition of nocturnal polyuria is age dependent and the thresholds for this diagnosis range from 20% (in younger persons) to 33% (age > 65 years) of the 24-hour urine volume produced during sleep. This may also be observed in patients with loss of circadian rhythm, cardiovascular disease, sleep apnoea, or sleep disorders [629]. A large study conducted across European and American centres involving ~2000 patients identified nocturnal polyuria as a contributory cause of nocturia in 89% of patients who were being treated for LUT abnormalities such as OAB syndrome or benign prostatic enlargement [634].

As an alternative to the ≥ 3-day bladder diary a nocturnal-only diary has been investigated in men [635]. The results showed acceptable sensitivity and specificity for the nocturnal bladder diary compared with the standard bladder diary for most parameters. The nocturnal-only diary was not able to diagnose 24-hour polyuria and has not yet been validated for use in women.

4.6.3.1 Summary of evidence and recommendations for diagnosis of nocturia

Summary of evidence	**LE**
A thorough medical history is an integral part of the evaluation of women presenting with nocturia.	4
Nocturia-specific questionnaires are sensitive to symptom changes.	3
A bladder diary allows for calculation of important indices and can identify potential causes of nocturia.	3
Nocturnal-only bladder diaries have been evaluated in men only.	3

Recommendations	**Strength rating**
Take a complete medical history from women with nocturia.	Strong
Use a validated questionnaire during assessment of women with nocturia and for re-evaluation during and/or after treatment.	Weak
Use a three-day bladder diary to assess nocturia in women.	Strong
Do not use nocturnal-only bladder diaries to evaluate nocturia in women.	Weak

*4.6.4 **Disease management***

When evaluating the results of trials involving treatment strategies for nocturia, it is vital to examine for clinical significance as statistical significance can be achieved with small reductions in nocturia episodes.

4.6.4.1 Conservative management

The individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. Interventions such as those listed below may help with nocturia but, for the majority, no quantification of their effect is possible:

- reduction of fluid intake at specific times;
- avoidance/moderation of intake of caffeine or alcohol;
- distraction techniques;
- bladder retraining;
- pelvic floor muscle training;
- reviewing medication;
- treatment of constipation.

The available data for conservative treatment of nocturia show significant heterogeneity. In the EAU SR [636], three studies [637-639] were favourable for conservative treatment with PFMT, with another failing to confirm a benefit [640].

The highest level of evidence comes from a study of 131 patients (a secondary analysis from a prospective RCT that had urgency-predominant UI as the primary inclusion criterion). The study found that training in PFM

contraction, which included four sessions of biofeedback-assisted PFMT reduced nocturia by a median 0.50 episodes per night and was significantly more effective than anticholinergic drug treatment or placebo [637]. The certainty of evidence associated with this treatment is moderate.

A smaller RCT of 50 women with urinary complaints, randomised 1:1 to bladder training and PFMT compared with a control group receiving no treatment, showed a significant decrease in patients' complaints of nocturia [638]. Another RCT in only 24 women compared PFMT only to transcutaneous electrical nerve stimulation therapy plus PFMT [639]. Although the authors did not find significant differences between the groups, the change in nocturia episodes before and after treatment was statistically significant in both groups. This study [641] was underpowered by the authors' own admission. The level of certainty of the evidence from these two trials is low. A large randomised, two-arm, parallel design, superiority trial (n = 647; women), compared the effects of unsupervised behavioural PFMT programs delivered in a two-hour class format and 20 minutes video format on UI prevention. No significant between-group differences of nocturia were observed at three months and twelve months, but at 24 months, women in the two hour class group were less likely to have fewer nocturia episodes (OR: 0.5; 95% CI: 0.3-0.7; p = 0.005) compared with those in the 20 minutes video group, but the authors concluded that the evidence is not sufficient to support one management strategy [642].

A multicentre, open-labeled, RCT evaluated whether cognitive behavioural therapy (CBT) using a self-assesment via a checklist is effective in improving nocturia in a mixed population (30/78 women). The mean rate of achievement of the CBT group was 64.4%. There was no significant difference between the two groups in night-time frequency based on the IPSS Q7 at four weeks but episodes of nocturia on the frequency volume chart (FVC) were significantly smaller in the CBT group (1.9 ± 0.9) than in the control group (2.4 ± 1.3; p = 0.039) [643].

In a secondary analysis from a prospective RCT, 210 women with UUI were evaluated for change from baseline in the number of episodes of nocturia and nocturnal incontinence between groups allocated to medical treatment (tolterodine ER 4 mg) alone vs. medical treatment plus PFMT [640]. No significant difference between the groups was found and the actual difference in nocturia episodes in either treatment arm was small. The level of certainty of the evidence from this trial is low.

A recent RCT has explored both individual and group PFMT with a specific secondary outcome of number of patients with two or more nocturia episodes per night [344]. The authors reported similar reductions, with > 30% of patients who had ≥ 2 episodes of nocturia at baseline no longer experiencing this level of symptoms at one year after PFMT.

One small, single-centre RCT in which functional magnetic stimulation was compared with no treatment in 39 women reported a significant decrease in nocturia (together with voiding frequency and pad use) in the treatment group compared with the control group [644].

In patients with obstructive sleep apnoea who complain of nocturia, continuous positive airway pressure has been shown to be effective in a SR and meta-analysis of five RCTs involving both sexes [645]. This treatment was associated with an average numerical reduction in nocturia of > 2 episodes per night.

4.6.4.1.1 Summary of evidence and recommendations for the conservative management of nocturia

Summary of evidence	**LE**
Individual or group PFMT appears to be equally effective for reduction in nocturia episodes.	1b
Most studies evaluating PFMT for nocturia in women with additional urinary symptoms have shown positive results compared with placebo or anticholinergic drugs.	1b
Treatment of nocturia secondary to obstructive sleep apnoea with continuous positive airway pressure reduces nocturia episodes.	1a

Recommendations	**Strength rating**
Offer women with lower urinary tract symptoms (LUTS) lifestyle advice prior to, or concurrent with, treatment.	Strong
Offer pelvic floor muscle training for nocturia (either individually or in the group setting) to women with urinary incontinence or other storage LUTS.	Strong
Offer women with nocturia and a history suggestive of obstructive sleep apnoea a referral to a sleep clinic for assessment of suitability for continuous positive airway pressure treatment.	Strong

4.6.4.2 Pharmacological management

4.6.4.2.1 Desmopressin

Desmopressin is a synthetic analogue of the hormone vasopressin and is most often used for management of nocturia due to nocturnal polyuria. In a recent SR [636], three trials specifically conducted in women were found but more additional data could be extracted from studies in mixed populations. The earliest evidence comes from a 1982 single-site crossover trial involving 25 women treated with 20 µg desmopressin or placebo and revealed a significant decrease in nocturnal urine output at six weeks [646]. A more recent multicentre, multinational double-blind RCT involving 141 women used desmopressin 0.1, 0.2 or 0.4 mg orally at bedtime after a dose-titration period [647]. This increased the likelihood of a positive outcome because non-responders were excluded at that stage. At three weeks, significant reductions in nocturnal urinary frequency and nocturnal diuresis were reported. In another multicentre double-blind RCT, 58 women were randomised into five groups (twelve receiving placebo, twelve desmopressin 10 µg, eleven desmopressin 25 µg, eleven desmopressin 50 µg and twelve desmopressin 100 µg) for four weeks [648]. A dose–response relationship was observed and women appeared more sensitive than men to desmopressin. Significant changes in nocturnal urine volumes were reported in favour of the higher desmopressin doses. Differences in the nocturnal polyuria index also tended to favour desmopressin over placebo and the higher desmopressin doses. The level of certainty of the evidence from these trials is low.

Desmopressin can be safely combined with anticholinergics with significant benefit in women with OAB and nocturnal polyuria, as shown by a multicentre RCT of 97 patients [649]. A *post hoc* analysis of data comparing three-month once-daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57) revealed a significant reduction in nocturnal void volume and time to first nocturnal void in favour of combination therapy. The level of certainty of the evidence from this trial is moderate.

Pooled data from three RCTs were used to examine the adverse event profile of desmopressin, specifically hyponatraemia [650]. The authors reported that the majority tolerate desmopressin treatment without clinically significant hyponatraemia, but risk increased with age and lower baseline serum sodium concentration. They advised that desmopressin treatment in elderly patients should include careful monitoring of the serum sodium concentration and should be avoided in patients with a baseline serum sodium concentration below normal range [650].

4.6.4.2.2 Anticholinergics

A SR [636] identified three RCTs involving anticholinergics such as oxybutynin 2.5 mg/day [637] and tolterodine 4 mg/day [640, 649]. A secondary analysis from a prospective RCT involving 131 women with nocturia followed up for eight weeks found that women receiving 2.5 mg immediate-release oxybutynin once daily (with the possibility of self-titration and dose escalation to 5 mg three times daily) had fewer nocturia episodes than women receiving placebo [637]. Women receiving oxybutynin plus behavioural therapy also exhibited a significant decrease in nocturia episodes compared with placebo and oxybutynin alone. A multicentre RCT with 305 women followed up for eight weeks examined the efficacy of tolterodine tartrate 4 mg alone or in combination with behavioural training [640]. Significant differences compared with baseline were observed in mean nocturia episodes and nocturnal incontinence episodes in both groups, but no difference was reported between the two treatment groups. The level of certainty of the evidence from this trial is moderate.

In an RCT including 97 women with nocturnal polyuria and OAB syndrome, comparing three months of once daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57), a significant reduction in mean number of nocturnal voids compared with baseline was reported in both groups [649]. The level of certainty of the evidence from this trial is moderate.

A large comparative study followed 407 women with OAB and nocturia for four weeks [651]. The patients were given tolterodine as monotherapy in one group, and tolterodine combined with estazolam (a benzodiazepine) in the other group. Significant changes from baseline in both groups for the main outcome of number of nocturia episodes were reported. Combination therapy showed a significant benefit for women with OAB and nocturia compared with monotherapy in terms of differences in number of nocturia episodes, urgency episodes in 24 hours, UUI episodes in 24 hours, and voided volume per micturition. The level of certainty of the evidence from this trial is very low.

A small multicentre RCT compared oxybutynin patch vs. mirabegron on nocturia-related QoL in women with OAB. Both treatments showed improvements in N-QoL score at four weeks, but mirabegron showed statistical differences at eight weeks. Additionally, only mirabegron decreased nocturnal frequency and water intake, and prolonged hours of uninterrupted sleep eight weeks after administration with statistical significance, whereas oxybutynin patch did not [652].

4.6.4.2.3 Oestrogens

In a recent SR [636] only a single RCT investigating the efficacy of oestrogen for nocturia was identified [653]. This trial compared an oestradiol-releasing vaginal ring with an oestriol vaginal pessary in 251 women followed up for six months. There was no difference between the treatment groups in the number of women reporting nocturia, although they reported significant change from baseline in both treatment arms with > 50% of subjects responding in each arm. The certainty of evidence for this outcome was low.

4.6.4.2.4 Diuretic treatment

In a randomised placebo-controlled study an afternoon dose of 40 mg furosemide (taken six hours before bedtime) in an attempt to establish complete diuresis before bedtime was given to elderly men [654]. In the 43 men who completed the study, night-time frequency in the furosemide group fell by 0.5 episodes compared with placebo, and percentage night-time voided volume fell by 18%. No such study has been carried out in female patients.

4.6.4.3 Summary of evidence and recommendations for pharmacological management of nocturia

Summary of evidence	**LE**
Desmopressin treatment for nocturia shows significant reductions in nocturnal urine output, nocturnal urinary frequency and nocturnal polyuria index.	1b
Most nocturia patients tolerate desmopressin treatment without clinically significant hyponatraemia; however, the risk increases with increasing age and decreasing baseline serum sodium concentration.	1a
Treatment of nocturia in OAB patients with anticholinergic drugs shows reduction in nocturia episodes.	1b
Combination of PFMT and pharmacological treatment with anticholinergics does not appear to confer additional benefit over anticholinergics alone.	1b
Combination of anticholinergic and desmopressin treatment appears to reduce nocturnal voided volume and time to first nocturnal void in women with nocturnal polyuria.	1b
Vaginal oestrogen may be beneficial in the treatment of nocturia in around 50% of women.	1b
Afternoon (timed) diuretic treatment with furosemide reduces nocturia episodes and nocturnal voided volume in men but no similar studies have been conducted in women.	1b
Examination for clinical significance is important when evaluating trials involving treatment strategies for nocturia, as statistical significance can be achieved with small reductions in nocturia episodes.	3

Recommendations	**Strength rating**
Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women, following appropriate counselling regarding the potential benefits and associated risks (including hyponatraemia).	Strong
Carefully monitor serum sodium concentration in elderly patients treated with desmopressin. Avoid prescribing desmopressin to patients with a baseline serum sodium concentration below normal range.	Strong
Offer anticholinergic treatment for nocturia to women with urgency urinary incontinence or other lower urinary tract symptoms, following appropriate counselling regarding the potential benefits and associated risks.	Strong
Inform women with nocturia that combination of behavioural therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone.	Weak
Offer combination of anticholinergics and desmopressin to women with overactive bladder and nocturia secondary to nocturnal polyuria, following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer vaginal oestrogen treatment to women with nocturia, following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer timed diuretic treatment to women with nocturia secondary to polyuria, following appropriate counselling regarding the potential benefits and associated risks.	Weak

4.6.4.4 Surgical management

Surgical treatment is generally reserved for those with underlying correctable LUT disorders. The effect of surgical treatments on symptoms of nocturia can be found in the relevant condition-specific sections of this guideline.

4.6.5 ***Follow-up***

Follow-up of patients with nocturia is dependent on the underlying aetiology of this symptom and the treatment given.

4.7 Pelvic organ prolapse and lower urinary tract symptoms

4.7.1 Epidemiology, aetiology, pathophysiology

Pelvic organ prolapse is a common condition in adult women. The prevalence of POP is 3–6% when bothersome symptoms are used to characterise the condition and increases to 50% when a purely anatomical definition is used [655].

The estimated lifetime risk for POP surgery is 12.6% [656]. Parity, vaginal delivery, ageing and obesity are the most commonly recognised risk factors [657].

Although the aetiology of POP is not fully understood, birth trauma to the levator ani complex is recognised as central to its development. In normal physiology, an intact levator ani complex functionally closes the genital hiatus surrounding the vagina, limiting the pressure gradient between the intra-abdominal and intravaginal areas. During physical activities, this reduces stress on the endopelvic fascia and its condensations (e.g., ligaments), which are crucial in securing the bladder, uterus and rectum to their surroundings. Current aetiological concepts include widening of the levator hiatus due to birth trauma, which creates a low-pressure area in the vagina and consequently increased stress on the ligaments, fascial elements and PFMs during physical activity. When the supporting function of the muscles and connective tissues fails, POP may develop [658]. This concept also explains the time lapse between birth trauma and occurrence of POP.

Pelvic organ prolapse and LUTS often occur simultaneously in women. In isolation, both POP and LUTS are prevalent conditions in women, although the prevalence of LUTS in women with POP exceeds that of LUTS in women without POP [655]. The observation that LUTS may improve or worsen after POP treatment suggests a link between these two entities [655]. Clinical examples include the occurrence of BOO symptoms in severe POP, and disappearance of SUI symptoms with progression of POP (and conversely the occurrence of SUI after treatment of POP) [659].

4.7.2 Classification

Since 1996, POP has been classified according to the Pelvic Organ Prolapse-Quantification (POP-Q) system [660]. For specifics on how to perform the POP-Q measurement and the nine standard points to be measured (Figures 2 and 3), we refer to the original publications [660, 661].

The vagina is divided into anterior (bladder), posterior (rectum) and apical (cervix or vaginal vault) compartments. After scoring the position of the nine POP-Q points, a prolapse of each compartment is graded numerically from stage 0 to 4, with stage 0 being no prolapse and stage 4 being complete eversion of the compartment. A crucial marker in staging POP is the hymenal remnant. Any POP with a maximum descent that is still 1 cm above the hymen (e.g., in the vagina) is considered a stage 1 POP. A maximum descent between 1 cm above and 1 cm below (outside the vagina) the hymen is a stage 2 POP. Any descent beyond 1 cm below the hymen is a stage 3 POP.

The figures below show the POP-Q staging in comparison to the Baden–Walker system (and others) used before the international consensus on the POP-Q staging was introduced as the new standard.

Figure 2: Prolapse classification system

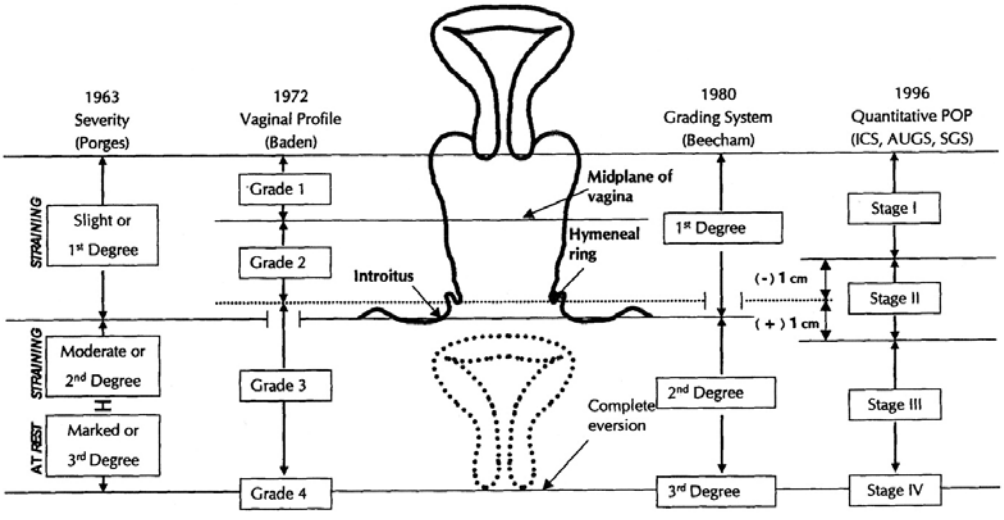


Figure reproduced with permission from the publisher, from Theofratus JP et al. [630].

Figure: 3: Pelvic Organ Prolapse-Quantification staging

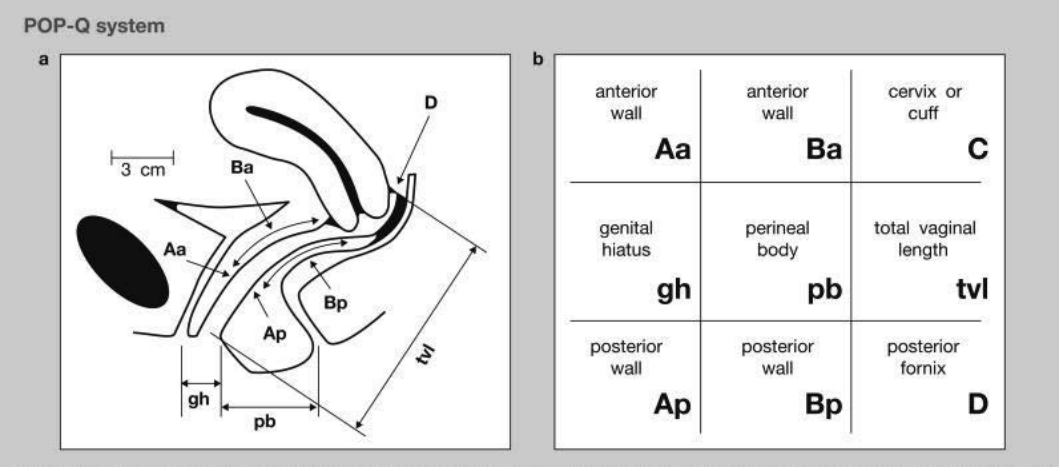


Figure reproduced with permission from the publisher, from Bump RC et al, [629]. The standardisation of terminology of female POP and pelvic floor dysfunction.

4.7.3 ***Diagnostic evaluation***

Pelvic organ prolapse is a clinical diagnosis and is staged according to the POP-Q system. Pelvic organ prolapse that is above the hymen should only produce mild symptoms at most [662]. In cases where there is a discrepancy between the clinical symptoms and POP-Q staging, it is advised to consider performing the POP-Q measurement in a standing rather than supine position, or re-evaluating at a later time in the day. Magnetic resonance imaging assessment demonstrated a marked difference in POP staging between supine and standing position [663]. Additional diagnostic tests for POP are mainly indicated if there are accompanying symptoms like LUTS or bowel dysfunction. Imaging techniques are not advised for the routine diagnostic work-up of patients presenting with POP [67]. The role of urodynamics in the diagnostic work-up of SUI has been discussed in the SUI, Section 4.2, of this guideline.

The use of techniques to reduce POP during urodynamic evaluation to diagnose occult SUI is common practice. This information may be used to decide if additional anti-UI surgery should be offered at the time of POP surgery or to counsel patients on the possible after-effects of POP treatment.

There are several POP reduction methods that may be used during physical examination or urodynamic evaluation. In a multicentre observational study, five different cough/stress tests were compared for their ability to detect SUI in women with POP [664]. Stress urinary incontinence during at least one of the five tests occurred in 60/205 (29.2%) women without SUI symptoms. Looking at single test performance, the detection rate of occult SUI in women without symptoms increased from 4.4% in case of no reduction to 22% in case of reduction with a pessary.

A large randomised trial included women with POP without symptoms of SUI, who were randomised to sacro-colpopexy with or without Burch colposuspension [665]. Three hundred and twenty-two stress-continent women with stages 2–4 prolapse underwent standardised urodynamic testing, and the protocol included five prolapse reduction methods. Preoperatively, twelve of 313 (3.7%) women demonstrated urodynamic SUI without prolapse reduction. Preoperative detection of urodynamic SUI with prolapse reduction at 300 mL was by pessary, 6% (5/88); manual, 16% (19/122); forceps, 21% (21/98); swab, 20% (32/158); and speculum, 30% (35/118). Another large trial included women with POP without SUI symptoms randomised to vaginal POP surgery with or without (sham incision) MUS [666]. Before surgery, 33.5% (111/331) of women demonstrated SUI at a prolapse-reduction cough stress test. In an observational study of 172 women with POP without SUI, 19% of women were diagnosed with occult SUI by basic office evaluation (with prolapse reduction with swab on forceps) and 29% on urodynamic evaluation [667].

In summary, SUI can be demonstrated in women with POP without symptoms of SUI after POP reduction in up to 30% of cases. There is no consensus on the best reduction technique.

Although the detection rate of occult SUI increases after reduction of POP in women without SUI symptoms, its clinical value is under debate.

In one trial, preoperative stress-continent women were evaluated during urodynamic testing with prolapse reduction to determine if they were more likely to report postoperative SUI, regardless of concomitant colposuspension (controls 58% vs. 38% and Burch colposuspension 32% vs. 21%) [665]. In another trial, women with SUI during the cough stress test after POP reduction reported UI at three months in 29.6% in the synthetic MUS group, compared with 71.9% in the sham group [666]. Women with a positive prolapse reduction stress test before surgery appeared to receive more benefit from a synthetic MUS at three months, but not at twelve months, than did those with a negative test.

In a large observational study, women did not receive additional anti-UI surgery even if they had SUI after POP reduction preoperatively. In this scenario, 9% (16/172) of women developed postoperative *de novo* SUI and six underwent surgery for *de novo* SUI [667]. Women with demonstrable preoperative SUI were more at risk of postoperative SUI: 28% vs. 5%. Based on urodynamic evaluation only, one more woman was predicted to have postoperative SUI, but all six women who underwent treatment for *de novo* SUI showed SUI during basic office evaluation.

In a model developed to predict the risk of *de novo* SUI in women undergoing POP surgery based on findings from two trials, twelve preoperative predictors were tested [668]. Positive SUI during a preoperative prolapse reduction test was included in this model, but it failed to be a significant predictor as a single item. Preoperative POP stage was not associated with risk of *de novo* SUI.

4.7.3.1 Summary of evidence and recommendation for detection of SUI in women with POP

Summary of evidence	**LE**
Pelvic organ prolapse reduction during cough stress test, in office or during urodynamics detects SUI in ~30% of continent women.	2a
Women with SUI after POP reduction preoperatively (occult SUI) are likely to be at increased risk of developing SUI symptoms after POP surgery.	2a

Recommendation	**Strength rating**
Perform pelvic organ prolapse (POP) reduction test in continent women to identify those with occult stress urinary incontinence and counsel them about the pros and cons of additional anti-incontinence surgery at the time of POP surgery.	Strong

4.7.3.2 Urodynamics in women with pelvic organ prolapse and LUTS (without stress urinary incontinence)

The role of urodynamics is less clear in women presenting with POP and concurrent LUTS, other than SUI. Pelvic organ prolapse is a complex condition incorporating different compartments of the vagina, and presenting at different stages of severity. Information about detrusor activity, as assessed with urodynamics, may provide information about the risk of developing DO after surgery, but also on the risk of urinary retention due to DU. An observational study assessed predictors for DO following POP surgery for POP-Q stage three or higher in 1503 women and the authors concluded that preoperative maximum urethral closure pressure ≥ 60 cm H_2O, Qmax < 15 mL/s, maximum detrusor voiding pressure (Dmax) > 20 cm H_2O and PVR volume > 200 mL were independent risk factors for postoperative DO [669]. A small observational study (n = 49) evaluated patients with preoperative DU (detrusor pressure at maximum flow was ≤ 10 cm H_2O and Q_{max} ≤ 12 mL/s) after POP surgery. Surgery objectively cured DU in 47% of women and urodynamic findings normalised after surgery [670]. The 2019 NICE guidelines do not include a recommendation to perform urodynamics as part of the diagnostic work-up of POP, except for combination with symptomatic SUI [67].

*4.7.4 **Disease management***

Pelvic organ prolapse symptoms can be treated with PFMT, vaginal pessary, surgery or a combination of these treatments. The scope of these guidelines is to focus on LUTS in women; therefore, only data on the effect of treatment of urinary symptoms are presented.

4.7.4.1 Conservative management of pelvic organ prolapse

The 2013 NICE guideline on Urinary Incontinence and POP in Women had an updated management section in 2019, including a full evidence review [67]. The overall conclusion with respect to conservative treatment for POP was that the evidence is of low quality. Thirteen RCTs were identified. Seven studies presented data on changes in urinary symptoms [671-677]. An additional search identified four RCTs that addressed the addition

of PFMT to POP surgery [678-681], and one that compared combined PFMT/Pilates therapy with lifestyle advice by leaflet [682].

Five studies [672, 674-676, 682] compared PFMT to lifestyle advice/leaflet; one study [673] compared PFMT alone to PFMT with pessary; one study [677] compared PFMT to pessary therapy; and five studies compared surgery for POP with or without addition of PFMT [671, 678-681].

4.7.4.1.1 Pelvic floor muscle training versus lifestyle advice

An RCT (n = 109) reported that, at six months' follow-up, the ICIQ-UI-SF scores improved in favour of the PFMT group compared with a control group receiving lifestyle advice only (difference from baseline PFMT 2.40 points and control 0.2 points) [672]. However, the difference of 2.4 points from baseline, in favour of PFMT, has to be viewed with caution as the mean baseline score in the PFMT group was higher than in the control group (7.4 vs. 5.9). Likewise, it has to be noted that the absolute ICIQ-UI-SF values at six months' follow-up were not significantly different between PFMT (4.8) and controls (5.2).

Two publications from one RCT reported on the three-, six- and twelve-month results of lifestyle advice only vs. lifestyle advice combined with group PFMT [674, 675]. The Urogenital Distress Inventory-6 (UDI-6) and Urinary Impact Questionnaire-7 (UIQ-7) questionnaires were used to assess urinary symptoms. At three months' follow-up, both groups (53 women in the lifestyle group and 56 in the lifestyle + PFMT cohort) reported significantly improved UDI-6 scores, while the lifestyle-only group also reported significantly greater improvement in the UIQ-7 score. Between-group comparison showed no differences in UDI-6 and UIQ-7 scores at six months. At twelve months' follow-up, the majority of women had sought additional treatment (70% in the lifestyle-only group and 48% in the lifestyle/PFMT group). The number of patients remaining on the original therapy was too small to reach strong conclusions.

One RCT reported on six and twelve months' follow-up of 225 women with POP-Q stage 1–3 randomised to individualised PFMT and 222 women randomised to lifestyle leaflet information only (control) [676]. Urinary symptoms were assessed with a single question on the existence of UI; a single question regarding the need to strain to void; and a single question regarding incomplete bladder emptying; these were supplemented with the ICIQ-SF questionnaire score. At six months, significantly more women in the control group reported UI, the need to strain to empty their bladder, and the feeling of incomplete emptying compared to the PFMT group. The score on the ICIQ-SF was also significantly worse in the control group as compared to the PFMT group. However, at twelve months, there was no significant difference in these items between groups. It has to be noted that 50% in the control group received additional treatment within the twelve-month study period. Twenty-seven percent had additional PFMT, which may have had an effect on the twelve-month data.

Another RCT reported on the 24-month follow-up of 414 women with stage 1–3 POP (207 assigned to PFMT/Pilates and 207 to lifestyle advice) [682]. Urinary symptoms were assessed with the ICIQ-UI-SF and a question about UI and difficulty emptying the bladder. At 24 months, the ICIQ-UI-SF score was significantly better in the intervention group (mean difference –0.83). However, the proportion of women reporting any UI did not differ between the groups, nor did the number of pads used weekly.

4.7.4.1.2 Pelvic floor muscle training versus pelvic floor muscle training with pessary

One RCT compared PFMT alone to PFMT and pessary for symptomatic POP [673]. Urinary tract symptom changes were assessed using UDI-6 and UIQ at six and twelve month's follow-up. At twelve months, there was no difference in the between-group comparison. With respect to the UIQ, women in the pessary/PFMT group showed a significant improvement from baseline, but the PFMT-only group did not. Women in the pessary/PFMT group reported significantly more frequent *de novo* SUI (48% vs. 22%), and more improvement of pre-existing voiding difficulty (62.5% vs. 35.5%).

4.7.4.1.3 Pelvic floor muscle training versus pessary only

One RCT reported on the 24-month follow-up of 82 women with symptomatic POP randomised to pessary therapy and 80 women randomised to PFMT [683]. The UDI-6 was used as the outcome measure for urinary symptoms. Both in the ITT and per protocol analyses, the UDI score did not differ significantly between groups at 24 months of follow-up.

4.7.4.1.4 Surgery alone versus surgery with pelvic floor muscle training

An assessor-blinded RCT compared surgery for POP with or without additional pre-and postoperative PFMT. At twelve months after surgery, there were no significant differences between the groups on the change in scores of the UDI nor the IIQ scores [671].

Another RCT reported on the six-month follow-up of 57 women (28 surgery/29 surgery with PFMT). The UDI-6 was used to assess urinary symptoms. There was a significant improvement in the UDI-6 score for both groups, but not between groups [679].

Another RCT reported on the results of a 2x2 factorial design in which women were first randomised between two surgical techniques for POP and between additional PFMT (n = 188) or not (n = 186) [680]. The UDI was used to assess urinary symptoms up to 24 months. No significant differences were found between the addition of PFMT to surgery or not. Another study of the same population reported on SUI in particular [681]. No significant differences were found between women who had additional PFMT and those who had not.

In 2020 an RCT reported on 40 and 90 days' follow-up of 48 women randomised to supervised PFMT before and after surgery and 40 women having surgery only [678]. UDI-6 was used to assess urinary symptoms. No significant differences in UDI-6 scores were identified at 40 and 90 days.

The NICE guidelines on the management of POP advocate considering supervised PFMT for ≥ 16 weeks as initial treatment for symptomatic prolapse [67]. The use of pessary is also to be considered, alone or combined with PFMT. It is important to recognise that a benefit is expected on typical POP symptoms, like feeling or seeing a bulge out of the vagina, and not on LUTS, as the reported RCTs showed. From a urological perspective, initiating conservative treatment for asymptomatic POP in order to treat UI or bladder emptying problems is not supported by the data.

4.7.4.1.5 Pessary versus surgery alone

A prospective cohort study showed that surgery in comparison with pessary treatment resulted in statistically significant more women reporting subjective improvement [684].

4.7.4.1.6 Summary of evidence and recommendation for the conservative treatment of pelvic organ prolapse and lower urinary tract symptoms

Summary of evidence	**LE**
Pelvic floor muscle therapy improves LUTS for up to six months in POP patients who do not have additional pessary or surgical treatment.	2a
If pessary therapy or surgical intervention is used for POP, PFMT does not show an additional benefit.	2a

Recommendations	**Strength rating**
Inform women with pelvic organ prolapse (POP), who do not need a vaginal pessary or surgical intervention, about the potential relief from lower urinary tract symptoms (LUTS) from pelvic floor muscle therapy (PFMT).	Strong
Do not offer preoperative PFMT to improve outcome of LUTS if pessary therapy or surgical intervention is indicated for POP.	Strong

4.7.4.2 Pelvic organ prolapse surgery and overactive bladder

Only a few studies have specifically addressed the effect of POP surgery on OAB symptoms. A SR of twelve studies, excluding women with SUI, evaluated OAB symptoms before and after surgery [685]. All but one study reported improvement of OAB symptoms. The same authors performed a prospective analysis of 505 women who had POP surgery with or without mesh [686]. Symptoms were assessed with UDI questions and each symptom was dichotomised into not bothersome or bothersome. Mean follow-up was 12.7 months. The incidence of bothersome urinary frequency reduced from 36.6% to 14.6%, with *de novo* symptoms occurring in 6.1% of women. Bothersome urgency symptoms reduced in 36.8% to 12.9% of women, with 5.0% developing *de novo* symptoms. Urgency urinary incontinence symptoms reduced from 21.2% to 6.1% of women, with 5.3% developing *de novo* symptoms.

One observational study evaluated frequency and urgency symptoms without consideration of bother in 87 women undergoing POP surgery and showed an improvement in frequency by 75%, and in urgency in 83% [687]. The effect of the POP-Q stage did not seem to influence the effect of surgery on OAB symptoms [686, 687].

Another observational study (n = 43) evaluated the effect of posterior repair on OAB/DO and showed a 70–75% improvement rate in both parameters after surgery [688].

4.7.4.3 Pelvic organ prolapse surgery and bladder outlet obstruction

The criteria for BOO are based on urodynamic assessment. Pelvic organ prolapse can be categorised as anatomical BOO, which is addressed in Sections 4.5.2.2 and 4.5.3.1.

4.7.4.4 Pelvic organ prolapse surgery and stress urinary incontinence

The aim of this section is to address the options available to women who require surgery for POP and who have associated SUI (either before or after reduction of prolapse), and to assess the value of prophylactic anti-UI surgery in women with no evidence of SUI.

A SR and meta-analysis of ten trials on prolapse surgery with or without an anti-incontinence procedure was reported in 2018 [689]. In addition, a Cochrane review including nineteen trials (n = 2,717) evaluating bladder function after surgery for POP presented analyses of women with POP and SUI, women with POP and occult SUI, and women with POP who were continent [690].

4.7.4.4.1 Vaginal pelvic organ prolapse surgery in women with stress urinary incontinence

Two trials addressed postoperative SUI in patients who had been diagnosed with SUI preoperatively and had vaginal POP surgery [691, 692]. Two trials (n = 185 and 134) compared the use of MUS at initial POP surgery to POP surgery alone. The RR for postoperative SUI was 0.30 in favour of the combined POP surgery and MUS group. One of these two trials also compared the use of MUS at initial POP surgery and at three months if SUI persisted [691]. At twelve months' follow-up, there was no difference between the groups regarding postoperative UI (RR 0.41); however, 44% of the women without initial MUS never required surgery and 29% were dry.

4.7.4.4.2 Abdominal pelvic organ prolapse surgery in women with stress urinary incontinence

One RCT randomised 47 women with POP and SUI to an abdominal POP surgical procedure; e.g., sacro-colpopexy with or without Burch colposuspension. Additional SUI surgery did not improve postoperative SUI as compared to sacro-colpopexy alone (RR: 1.38) [693]. This finding remained consistent over five years' follow-up [694]. Another RCT compared the addition of a MUS or Burch colposuspension to an abdominal sacro-colpopexy in 113 women with POP and SUI [695]. At two years' follow-up, the RR for postoperative SUI was 0.54 in favour of the MUS group.

4.7.4.5 Vaginal pelvic organ prolapse surgery in continent women

One RCT compared vaginal POP surgery alone with concomitant POP surgery and MUS in 220 women. Postoperative SUI occurred in 46/113 (40.7%) women who had POP surgery alone, compared to 30/107 (28.0%) who had additional MUS (RR: 0.69) [690].

4.7.4.5.1 Abdominal pelvic organ prolapse surgery in continent women

Two RCTs compared abdominal sacro-colpopexy with (n = 189) or without (n = 190) Burch colposuspension with an outcome favouring the addition of Burch colposuspension (RR for *de novo* SUI: 0.69) [696, 697].

4.7.4.5.2 Vaginal pelvic organ prolapse surgery in women with prolapse and occult stress urinary incontinence

Five RCTs including a total of 194 women who had vaginal POP repair alone and 174 women who had an additional MUS at the time of primary surgery were identified [666, 698-701]. The RR of postoperative SUI was 0.38 in favour of the MUS group.

4.7.4.6 Adverse events associated with combined pelvic organ prolapse and stress urinary incontinence surgery

Data from six RCTs on vaginal POP surgery with MUS were pooled to assess adverse events [666, 691, 692, 699-701]. Urgency urinary incontinence was less frequent after combination surgery as compared to POP surgery alone (28% vs. 42%; RR: 0.7), but there was a tendency towards more voiding problems. Adverse events directly related to surgery occurred more often in the combination group (28% vs. 15%; RR: 1.8), as did serious adverse events such as bladder perforation, urethral injuries, and tape exposure (14% vs. 8%; RR 1.7) [689].

In summary, it is difficult to generalise the results of trials using different procedures to treat both POP and UI. It seems that with a combined procedure, the rate of postoperative SUI is lower but voiding symptoms and complication rates are higher. Studies using MUS have shown more significant differences in UI outcomes with combined procedures than when other types of anti-UI procedure have been used. It must be taken into account that although more women are dry after combined surgery for POP with MUS, there are potential adverse events that should be balanced against potential benefits.

4.7.5 *Summary of evidence and recommendations for surgery in women with both pelvic organ prolapse and stress urinary incontinence*

Summary of evidence	LE
Women with POP and UI	
Surgery for POP and SUI shows a higher rate of cure of UI in the short-term than POP surgery alone.	1a
There is conflicting evidence on the relative long-term benefit of surgery for POP and SUI vs. POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1a
Continent women with POP	
Continent women with POP are at risk of developing SUI postoperatively.	1a
The addition of a prophylactic anti-UI procedure reduces the risk of postoperative UI but increases the risk of adverse events.	1a
Women with POP and OAB	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of OAB.	2b

Recommendations for women requiring surgery for bothersome pelvic organ prolapse (POP) who have symptomatic or occult stress urinary incontinence (SUI)	**Strength rating**
Offer simultaneous surgery for POP and SUI only after a full discussion of the potential risks and benefits of combined surgery vs. POP surgery alone.	Strong
Inform women of the increased risk of adverse events with combined prolapse and anti-urinary incontinence surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome POP who do not have symptomatic or occult SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Warn women that the benefit of combined surgery for POP and SUI may be outweighed by the increased risk of adverse events compared to prolapse surgery alone.	Strong

4.8 Urinary fistula

The evidence relating to diagnosis and treatment of urinary fistulae is generally low level and largely composed of case series and other consensus statements. In particular, the epidemiology, aetiology, diagnosis, treatment and prevention of obstetric and non-obstetric fistulae have been described in detail during the 2016 ICI conference [702]. Most non-obstetric fistulae are iatrogenic in origin, with most caused by pelvic surgery (e.g., hysterectomy for benign or malignant conditions, bowel resection, and urological surgery). The risks during pelvic surgery increase relative to the complexity of the resection, the extent of primary disease, and prior radiotherapy (especially for recurrent disease). When a fistula occurs following radiotherapy for primary treatment, this may be an indication of tumour recurrence.

4.8.1 *Epidemiology, aetiology and pathophysiology*

4.8.1.1 *Obstetric fistula*

According to the WHO, fistulae affect > 2 million women, mostly from sub-Saharan African and Asian countries. The pooled prevalence of fistula from population studies is 0.29/1000 pregnancies [703]. Poor quality obstetric care, staff unaccountability, late referral, and poor nursing standards have been identified as health system causes [703]. However, obstructed labour is poorly documented. The main individual risk factors include age at first marriage, short stature, pregnancy with a male child, failure to attend antenatal care, low socio-economic status, low social class, lack of employment, and illiteracy [704-706]. Obstetric fistulae have detrimental consequences on global and individual health and are associated with malnutrition, sexual dysfunction, anxiety, depression, insomnia, social isolation, worsening poverty, and suicide [707, 708].

4.8.1.2 *Iatrogenic fistula*

Poor obstetric care is usually responsible for VVF in the developing world. By contrast, in the developed world, gynaecological or pelvic surgery is the main cause of VVF.

4.8.1.2.1 Post-gynaecological surgery

An injury to the urinary tract during hysterectomy for benign conditions (60–75%), hysterectomy for malignant conditions (30%) and caesarean section (6%) are the main causes of postoperative VVF in the developed world [709, 710]. The risk of pelvic organ fistula following hysterectomy ranges from 0.1 to 4% [711].

Fistulae may also occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, and/or chemotherapy.

In a study including 536 women undergoing radical hysterectomy for invasive cervical cancer, bladder injury occurred in 1.5% with VVFs forming in 2.6% and uretero-vaginal fistulae (UVFs) in 2.4% of cases [712]. Overall, the rate of urogenital fistula appears to be ~9 times higher following radical hysterectomy for malignant disease as compared to that following simple hysterectomy (abdominal or vaginal for benign conditions) [713]. Bladder-sparing techniques during pelvic exenteration can increase the risk of fistula formation [714].

4.8.1.2.2 Radiation fistula

The risk of fistula seems to be higher for postoperative external radiation (1.9%) compared to intravaginal brachytherapy (0.8%) [715], without any predictive factor being identified [716]. This is most likely due to the heterogeneity of data regarding the tumour type and stage, the form of radiation, and the site and dose delivered.

4.8.1.2.3 Rare causes of vesico-vaginal fistula

Foreign bodies such as pessaries, sex toys, cups etc. can be a cause of delayed presentation of VVF [717-719]. Ketamine abuse has also been shown to be responsible for fistula formation [720].

4.8.1.3 Summary of evidence for epidemiology, aetiology and pathophysiology of urinary fistula

Summary of evidence	**LE**
The risk of injury to the urinary tract and subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures.	2
The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment.	4

*4.8.2 **Classification***

Due to the plethora of VVF classification systems, a consensual classification system needs to be adopted. The Waaldijk and Goh classifications are widely used for diagnosis and follow-up [721-723]. They were originally designed for obstetric fistulae and their use in iatrogenic fistulae is less relevant [724]. Waaldijk's classification is based on the size and site of the fistulae and divides them into three main categories: type 1 are VVFs with no urethral involvement; type 2 are those that involve the urethra (and are sub-classified into those with circumferential and non-circumferential urethral involvement); and type 3 are fistulae involving other parts of the urinary tract. Goh's classification also uses the presence or absence of urethral involvement to sub-categorise VVFs and takes into account the degrees of fibrosis present. The WHO classification (Table 6) was originally developed for obstetric fistulae and separates fistulae into simple and complex.

Table 6: Adapted WHO Classification of fistulae [703]*****

Simple fistula with good prognosis	**Complex fistula with uncertain prognosis**
• Single fistula < 4 cm	• Fistula > 4 cm
• Vesico-vaginal fistula	• Multiple fistula
• Closing mechanism not involved	• Recto-vaginal mixed fistula, cervical fistula
• No circumferential defect	• Closing mechanism involved
• Minimal tissue loss	• Scarring
• Ureters not involved	• Circumferential defect
• First attempt to repair	• Extensive tissue loss
	• Intravaginal ureters
	• Failed previous repair
	• Radiation fistula

**Although this classification was developed for obstetric fistula initially, it could be relevant for iatrogenic fistula as well.*

4.8.2.1 Recommendation for the classification of urinary fistula

Recommendation	Strength rating
Use a classification system for urinary tract fistulae to try to standardise terminology in this subject area.	Strong

*4.8.3 **Diagnostic evaluation***

Leakage of urine is the hallmark sign of a urogenital fistula. The leakage is usually painless, may be intermittent if it is position dependent, but more usually is constant. Unfortunately, intraoperative diagnosis of a genito-urinary or gastrointestinal injury is made in only about half of cases [725]. Diagnosis of VVF usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection, cystoscopy, retrograde bladder filling with a coloured fluid, or placement of a tampon into the vagina to identify staining may facilitate diagnosis of VVF. A double-dye test to differentiate between UVF and VVF may be useful in some cases [710]. Testing the creatinine level in either the extravasated or collected fluid will confirm fluid leakage as urine. Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the possible presence of associated urinoma. Magnetic resonance imaging, in particular with T2 weighting, also provides diagnostic information regarding fistulae [726].

*4.8.4 **Disease management of fistula***

4.8.4.1 Management of vesico-vaginal fistula

4.8.4.1.1 Conservative management

4.8.4.1.1.1 Spontaneous closure

The reported spontaneous closure rate is 13 ± 23% [727], although this applies largely to small fistulae (< 1 cm) [702, 728]. Hence, immediate management is usually by urinary catheterisation or diversion; however, within the first two weeks following fistula occurrence, surgical exploration and repair can be considered.

4.8.4.1.1.2 Pharmacotherapy

Several case reports describe a successful fistula closure rate following the induction of amenorrhoea by oestrogen, oestrogen/progesterone combinations or luteinising hormone releasing hormone analogues specifically for small (< 7 mm), uretero- or vesico-uterine fistulae following caesarean section [729-735]. One RCT comparing the efficacy of using fibrin glue compared to Martius flap inter-positioning (n = 14; < 4 cm and n = 5; > 5 cm) did not report significantly different outcomes between the two types of treatment [736].

4.8.4.1.1.3 Palliation and skin care

During the intervening period between diagnosis and repair, UI pads with the aim of prevention of skin complications related to chronic urinary leakage can be provided and the use of a barrier cream or local oestrogen can also be considered [737, 738].

4.8.4.1.1.4 Nutrition

Nutritional support is essential in patients with fistulae induced by malignant disease or radiotherapy [739], or following diversion surgery [739-741].

4.8.4.1.1.5 Physiotherapy

Early involvement of the physiotherapist in preoperative management and rehabilitation of fistula patients suffering from limb weakness, foot drop and limb contracture is essential [742, 743].

4.8.4.1.1.6 Antimicrobial therapy

Active infection in the genital or urinary tracts should be treated prior to surgical repair [744].

4.8.4.1.1.7 Counselling

Confident and realistic counselling by the surgeon is essential and the involvement of nursing staff or counsellors with experience of fistula patients is also desirable.

4.8.4.1.2 Surgical management

4.8.4.1.2.1 Timing of surgery

Findings from uncontrolled case series suggest no difference in success rates for early (within three weeks) or delayed (after three months) closure of VVF.

4.8.4.1.2.2 Surgical approaches

Vaginal procedures

There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis [727] and the more commonly used dissection and repair in layers or flap-splitting technique [745]. There are no data comparing their outcomes.

Abdominal procedures

Repair by the abdominal route is indicated when high fistulae are fixed at the vaginal vault and are inaccessible via a vaginal approach. A transvesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often although it is favoured by some using the laparoscopic approach. A combined transperitoneal and transvesical procedure may be utilised for fistula repair following caesarean section. There are no RCTs comparing abdominal and vaginal approaches. Results of secondary and subsequent repairs are not as successful as the initial repair [746].

A single RCT compared trimming of the fistula edge with no trimming. There was no difference in success rates but failed repairs in trimmed cases had larger recurrences than untrimmed cases, which were smaller [747].

Laparoscopic and robotic procedures

Small series (single figures) have reported using these techniques, but while laparoscopic repair is feasible with and without robotic assistance, it is not possible to compare outcomes with alternative surgical approaches.

Tissue interposition

Tissue flaps are often added as an additional layer of repair during VVF surgery. Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischaemic or obstetric fistulae, large fistulae, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high-level evidence that the use of such flaps improves outcomes for either complicated or uncomplicated VVF.

Postoperative management

There is no high-level evidence to support any particular practice in postoperative management but most reported series used catheter drainage for ≥ 10 days and longer periods in complex or radiation-associated fistulae (up to three weeks). The performance of postoperative cystography prior to catheter removal can miss a persistent fistula if not done with a micturition phase or if the fistula is located at the bladder neck.

4.8.4.1.3 Management of complications of vesico-vaginal fistulae

The complications of VVF repair are varied and can include:

- Persistence or recurrence of fistula;
- Persistence or recurrence of UI;
- Persistence of LUTS or occurrence of new LUTS, including *de novo* overactive bladder symptoms and/or SUI;
- Infections: wound and UTIs/urosepsis;
- Ureteric obstruction (ligation, fibrosis or injury);
- Bladder outlet obstruction (meatal stenosis, urethral stricture or bladder neck obstruction);
- Bladder contracture;
- Vaginal stenosis;
- Sexual dysfunction (vaginismus/dyspareunia);
- Rare complications (granulomas/diverticulum formation);
- Neurological complications (foot drop/neurogenic bladder);
- Psychological trauma (social isolation/divorce/mental illness);
- Infertility.

The literature on the treatment and management of complications of fistula repairs is scarce and is mostly experience-based. It is impossible to provide any specific evidence-based guidance.

4.8.4.2 Management of radiation fistulae

Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer [748]. Due to the wide field abnormality surrounding many radiotherapy-associated fistulae, approaches include, permanent urinary and/or faecal diversion [748, 749] or preliminary urinary and faecal diversion, with later undiversion in selected cases following reconstruction. In cases where life expectancy is deemed to be short, ureteric occlusion might be more appropriate.

4.8.4.3 Management of ureteric fistulae

4.8.4.3.1 General principles

Patients at higher risk of ureteric injury require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and recognise injury promptly. Immediate repair of any intraoperative injury should be performed by observing the principles of debridement, adequate blood supply and tension-free anastomosis with internal drainage using stents [750]. Delayed presentation of UUT injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvicalyceal system.

While there is no evidence to support the use of one surgical approach over another, there is consensus that repair should adhere to the standard principles of tissue repair and safe anastomosis, and be undertaken by an experienced team. Conservative management is possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< 2 weeks) or delayed (> 3 months) surgical repair when required [751]. Functional and anatomical imaging should be used to follow-up patients after repair to guard against development of ureteric stricture and deterioration in renal function.

4.8.4.3.2 Uretero-vaginal fistulae

Uretero-vaginal fistula occurring in the early postoperative phase predominantly after hysterectomy is the most frequent presentation of UUT fistulae in urological practice. An RCT in 3141 women undergoing open or laparoscopic gynaecological surgery found that prophylactic insertion of ureteric stents made no difference to the low risk (1%) of ureteric injury [752].

Endoscopic management is sometimes possible by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or ureteroscopic realignment [753]. However, the long-term success rate is unknown. If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, reimplantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration. As a last resort, nephrectomy may be considered, particularly in the context of a poorly functioning kidney and an otherwise normal contralateral kidney [754-758].

4.8.4.3.3 Management of urethro-vaginal fistulae

4.8.4.3.3.1 Aetiology

Although urethro-vaginal fistulae are rare, most of them in adults have an iatrogenic aetiology. Causes include surgical treatment of SUI with bulking agents or synthetic slings, surgery for urethral diverticulum and genital reconstruction. Irradiation and even conservative treatment of prolapse with pessaries can lead to formation of fistulae.

4.8.4.3.3.2 Diagnostic evaluation

Clinical vaginal examination, including the three-swab test, is often sufficient to diagnose UVF. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistulae. In cases of difficult diagnosis, VCUG or US can be useful. An 3D-MRI or CT scan is becoming utilised more widely to clarify anatomy [759, 760].

4.8.4.3.3.3 Surgical management

Choice of surgery will depend on the size, localisation, and aetiology of the fistula and the amount of tissue loss. Principles of reconstruction include identifying the fistula, creation of a plane between the vaginal wall and urethra, watertight closure of the urethral wall, eventual interposition of tissue, and closure of the vaginal wall.

One case series reported that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, and that an abdominal approach only led to successful closure in 58% of cases [761]. A vaginal approach required less operating time, had less blood loss and shorter hospitalisation.

Most authors have described surgical principles that are identical to those of VVF repair, and primary closure rates of 53–95.4% have been described. A series of 71 women, treated for UVF reported that 90.1% of fistulae were closed at the first vaginal intervention. Additionally, 7.4% were closed during a second vaginal intervention. Despite successful closure, SUI developed in 52% of cases. Stress urinary incontinence patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation or urethrotomy [762].

4.8.4.3.3.4 Flaps and neo-urethra

The simplest flap is a vaginal advancement flap to cover the urethral suture line. Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect, but can also be used to create a tubular neo-urethra [763, 764]. The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases, a transpubic approach has been used [765]. The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbo-cavernosus tissue can be incorporated in the pedicled flap and probably offers better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome SUI would occur postoperatively [766, 767].

4.8.4.3.3.5 Martius flap

In obstetrical fistula repair, the Martius labial bulbocavernosus muscle/fat flap was not found to have any benefit. However, the Martius flap is still considered by some to be an important adjunctive measure in the treatment of genitourinary fistulae for which additional bulking with well-vascularised tissue is needed [768]. The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomised studies [769]. The indications for Martius flap in the repair of UVF remain unclear.

4.8.4.3.3.6 Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors [770, 771].

4.8.4.3.3.7 Alternative approaches

An alternative retropubic retro-urethral technique has been described by Koriatim [772]. This approach allows a urethro-vesical flap tube to be fashioned to form a continent neo-urethra.

4.8.4.4 Summary of evidence and recommendations for the management of urinary fistula

Summary of evidence	**LE**
Spontaneous closure of surgical fistulae does occur, and appears more likely for small fistulae although it is not possible to establish the rate with any certainty.	3
There is no evidence that the timing of repair makes a difference to the chances of successful closure of a fistula.	3
There is no high-quality evidence of differing success rates for repair of VVFs by vaginal, abdominal, transvesical, and transperitoneal approaches.	3
A period of continuous bladder drainage may be crucial to successful fistula repair but there is no high-level evidence to support one regimen over another.	3
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting.	3
Post-radiation fistula	
Successful repair of irradiated fistulae may require prior urinary diversion and the use of non-irradiated tissues to effect repair.	3
Ureteric fistula	
Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery.	2
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase.	4
Urethro-vaginal fistula	
Urethro-vaginal fistula repair may be complicated by SUI, urethral stricture and urethral shortening, which may necessitate long-term follow-up.	3

Recommendations	**Strength rating**
General	
When reporting on outcomes after fistula repair, authors should make a clear distinction between fistula closure rates and postoperative urinary incontinence rates and the time at which the follow-up was organised.	Strong
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	Strong

Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs postoperatively, or if drainage fluid contains high levels of creatinine.	Strong
Use three-dimensional imaging techniques to diagnose and localise urinary fistulae, particularly in cases with negative direct visual inspection or cystoscopy.	Weak
Manage upper urinary tract fistulae initially by conservative or endoluminal techniques where such expertise and facilities exists.	Weak
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills and experience to select an appropriate procedure for each patient.	Weak
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to, and following, fistula repair.	Weak
Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	Weak
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: ten to fourteen days for simple and/or post-surgical fistulae; fourteen to 21 days for complex and/or post-radiation fistulae).	Weak
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	Weak
Use interposition graft when repair of radiation-associated fistulae is undertaken.	Weak
Repair persistent uretero-vaginal fistulae by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence.	Weak
Urethro-vaginal fistulae should preferably be repaired by a vaginal approach.	Weak

4.9 Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion composed of the entire urethral wall or only the urethral mucosa, situated between the periurethral tissues and the anterior vaginal wall.

*4.9.1 **Epidemiology, aetiology, pathophysiology***

Urethral diverticulum is an uncommon condition with an estimated prevalence of 1–6%. A prevalence of up to 10% was reported among women with LUTS attending a tertiary referral centre [773]. However, as many patients are asymptomatic or misdiagnosed, the true incidence is unknown [774-776]. Given the rarity of the condition, most published series are small and single institutional. Urethral diverticulum is thought to arise from repeated obstruction, infection, and subsequent rupture of periurethral glands into the urethral lumen, resulting in an epithelialised cavity that communicates with the urethra [774].

Iatrogenic damage to the urethra may also play a role, as up to 20% of women with urethral diverticula are noted to have a history of urethral surgery, dilation, or traumatic delivery [774, 777]. Iatrogenic urethral diverticula formation associated with synthetic suburethral sling has also been reported [778-780].

*4.9.2 **Classification***

Table 7: Classification system for female urethral diverticula based on characteristics*

Localisation	Mid-urethral Distal Proximal Full length
Configuration	Single Multi-loculated Saddle shaped
Communication	Mid-urethral No communication visualised Distal Proximal
Continence	Stress urinary incontinence Continent Post-void dribble Mixed incontinence

**Limited LNS C3 classification of urethral diverticula [777, 781, 782].*

*4.9.3 **Diagnostic evaluation***

The commonly encountered symptoms for urethral diverticulum such as pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or UI [783], are common to many other LUT dysfunctions. Consequently, there is no pathognomonic cluster of symptoms to identify urethral diverticulum. Many patients with urethral diverticulum are asymptomatic. However, urethral diverticulum often presents with a palpable urethral mass. It may be possible to express a purulent exudate from the urethra. Occasionally a stone may develop within the diverticulum.

Urethral diverticulum can be diagnosed by physical examination, VCUG and MRI. Other investigations include urethrocystoscopy, endocavitary (often transvaginal or sometimes transurethral) pelvic floor US and double balloon urethrography.

No robust diagnostic accuracy studies have addressed the question of the best test to confirm the diagnosis in women with clinical suspicion of urethral diverticulum. However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than VCUG [784] and determines the size and extent of urethral diverticulum more accurately. A case series of 60 patients reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI was 100%, 83%, 92% and 100%, respectively [785]. Another case series reported 100% specificity and sensitivity of MRI in 60 patients [786]. However, a case series of 41 patients reported a 25% discrepancy between MRI and surgical findings [787]. Endoluminal MRI with either a vaginal or rectal coil may provide even better image quality than simple MRI [788].

Magnetic resonance imaging is the gold standard for the diagnosis and planning of surgical repair. Magnetic resonance imagine is also useful in diagnosing diverticular inflammation or tumour [789, 790].

Urethrocystoscopy can be used to visualise the ostia of the diverticula. Knowledge of the ostias' location and number can assist with surgical planning since they need to be closed after diverticulectomy. However, given the challenges of urethroscopy in women, the ostia are only seen in 42% of cases [783].

If VCUG is performed, antero-posterior and lateral images are required to optimally characterise the configuration of the diverticulum. There is a high risk of false negatives since the ostia of the diverticula must be patent and the patients must be able to void during the study. In more complex diverticula where there is septation, the entire diverticulum may not be visualised underestimating its complexity or size [791]. The sensitivity of VCUG is 73.5% which is significantly worse than MRI [783].

Ultrasound can be performed transabdominally, transvaginally or transperineally to identify the diverticulum. In particular, the transvaginal approach allows imaging of the urethra from the meatus to the bladder neck in several planes and can identify the number, size, location and contents of the diverticulum. This technique is challenging and requires a skilled ultrasonographer. Additionally, the probe can compress the urethra, causing distortion [791]. A meta-analysis reported that US of any kind had a sensitivity of 82.0%, which was inferior to that of MRI [791]. However, a recent publication on translabial US reported a sensitivity of 95% [792]; therefore, this approach may be explored further by researchers in the future.

For patients who cannot undergo MRI and those in whom the ostia cannot be seen on cystoscopy, double balloon urethrography is an option. Sensitivity of 94.7% has been reported, which is comparable to that of MRI. The technique uses positive pressure to force contrast medium into the diverticular sac between two balloons; one placed in the bladder and one outside the ostium of the diverticulum. It is technically difficult to achieve a seal sufficient to create a closed urethral space and avoid contrast medium leaking around the catheter. The procedure can be painful for the patient and carries a risk of UTI. An experienced radiologist is required as well as specialised equipment. Given the current popularity of other imaging modalities, many units may not have access to this technique [791].

4.9.3.1 Associated voiding dysfunction

Although the presentation of urethral diverticulum is often non-specific and variable, urethral diverticulum can be associated with voiding dysfunction and SUI or urgency UUI.

One recent series reported SUI in 60% of patients with urethral diverticulum [793]. Urethral diverticulum is most often located at the level of the mid-urethra. This location often overlaps with the external sphincter. However, urethral diverticulum may also extend proximally toward the bladder neck in the vicinity of the proximal sphincter mechanism. This morphology may, in part, explain the association between urethral diverticulum and SUI, with potentially more proximal lesions at risk for postoperative SUI [794].

Urethral diverticulum may also be associated with BOO due to the mass effect of the urethral diverticulum, urinary retention, or urgency and UUI [795]. Pain and dysuria associated with urethral diverticulum may also result in acquired voiding dysfunction.

Pressure–flow studies may have a role in the preoperative assessment of patients with urethral diverticula and coexisting voiding dysfunction or SUI [776, 796-798]. Indeed, urodynamics may evaluate coexisting detrusor dysfunction or document the presence of SUI or obstruction prior to repair [799, 800].

Urethral pressure profilometry has also been used in the assessment or diagnosis of urethral diverticulum, noting a biphasic pattern, or pressure drop at the level of the lesion [796, 798, 801]. Video-urodynamics may be helpful in differentiating SUI from paradoxical UI due to fluid accumulation in the urethral diverticulum. Additionally, resting and straining images obtained during fluoroscopic imaging may document an open bladder neck at rest. This may be a consideration in some patients with an extensive urethral diverticulum at the level of the mid-urethra, and potential implications for postoperative UI due to compromise of both sphincter mechanisms.

*4.9.4 **Disease management***

For women with minimal symptoms who would prefer to avoid invasive treatment, conservative management can be considered. Patients should be warned of the small risk of cancer (1–6%) within the diverticulum [802, 803].

4.9.4.1 Surgical treatment

No RCTs have investigated the effectiveness of surgery in women who have a bothersome urethral diverticulum. Thorough evaluation of the anatomy of the diverticulum is essential in planning reconstructive surgery.

There are three surgical approaches to treatment of diverticulum: marsupialisation, endoscopic incision, and curative treatment with diverticulectomy.

Surgical removal is the most commonly reported treatment in contemporary case series. The principles of successful transvaginal diverticulectomy are to: dissect a well-vascularised vaginal flap; preserve the periurethral fascia for closure; remove all the diverticular wall; excise the ostium and close the urethra in a watertight fashion; close the incision in a multilayered fashion with no overlapping suture lines; and preservation or creation of continence.

The decision to use a labial fat pad flap, commonly known as a Martius flap, varies, and the flap is used more frequently in the following situations: recurrent cases, large urethral defects or for deficient vaginal flaps for closure [777, 781] transection of the urethra required for access to a circumferential diverticulum [790] or in the case of complex configuration [795], and if there is a planned future sling procedure required for UI to facilitate the dissection at that time [777].

Marsupialisation involves incision into the mass on the vaginal side to drain the infected contents. The wall is sutured open with absorbable suture to allow drainage and prevent reaccumulation of infectious materials. This approach leaves the cystic structure in place and can theoretically cause a urethro-vaginal fistula because there is communication with the diverticular ostium, but it is a rapid procedure with little dissection required. This approach has been advocated in pregnant patients to decompress the diverticulum and allow safe vaginal delivery. A small case series suggested that 75% of pregnant women with urethral diverticula managed expectantly eventually required postpartum surgery [804].

Endoscopic incision is a rarely reported treatment option [805, 806]. This procedure involves finding the narrow neck of the ostium and incising it with a resectoscope. This unroofing of the diverticulum transforms the narrow communication with the urethra that causes symptoms when it becomes obstructed into a wide-mouthed sac that drains freely.

4.9.4.2 Management of concomitant stress urinary incontinence

Many women present with concomitant SUI and urethral diverticulum, and may request both conditions to be simultaneously treated. A meta-analysis reported that diverticulectomy cured SUI even without a concomitant anti-incontinence procedure. However, no data regarding symptom severity were given and it could be assumed that many of these cured patients had less-severe UI before surgery [783]. Therefore, additional surgical correction may be required [794, 806]. However, there is no consensus on appropriate timing of surgical management of these two conditions. Thus, patients with symptomatic bothersome SUI in

association with urethral diverticulum may be offered simultaneous anti-UI surgery. Although historical series have shown good results with concomitant bladder neck suspension [800], more contemporary series have utilised pubovaginal fascial slings, with satisfactory outcomes [807-810]. Synthetic MUS are not recommended as a concomitant anti-UI procedure at the time of urethral diverticulectomy [811]. Synthetic material adjacent to a fresh suture line following diverticulectomy in the setting of potentially infected urine may place the patient at higher risk for subsequent urethral erosion and vaginal extrusion of the sling material, as well as urethro-vaginal fistula formation and foreign body granuloma formation.

Transvaginal urethral diverticulectomy has a high success rate (defined by being dry) of 84–98%, with a reoperation rate of 2–13% after primary repair during a mean follow-up of twelve to 50 months [774, 777, 794, 812]. The resolution of symptoms after surgery has been reported to reach 68.8% but less than half of studies comment on symptom improvement [813]. One case series reported that storage symptoms decreased significantly postoperatively from 60% to 16% following surgery for urethral diverticulum [794]. Other series with long-term follow-up, however, have demonstrated rates of postoperative urgency of 54% [814], and *de novo* UUI in 36% of patients [806]. Such postoperative symptoms indicate persistence of urethral diverticulum, recurrence of urethral diverticulum, or *de novo* overactive bladder syndrome or urethral obstruction.

Early common postoperative complications include: UTI (0–39%), *de novo* SUI (3.8–33%), and *de novo* urinary retention (0–9%), especially in the setting of concomitant placement of an autologous pubovaginal sling [774, 777, 794, 812]. Delayed complications such as urethral stricture are reported in 0–5.2% of cases [774, 777, 806, 812]. Urethro-vaginal fistula is a devastating complication presenting in 0.9–8.3% of cases [815]. A distal fistula located beyond the sphincteric mechanism can present with split urinary stream or vaginal voiding and may not require repair. However, a fistula located anywhere from the mid-urethra to the bladder neck may result in UI. These patients should undergo repair with consideration of an adjuvant tissue flap, such as a Martius flap, to aid in closure. The timing of the fistula repair is not well defined, with a delay of three to six months after the initial repair being a good balance between patient discomfort and optimal tissue quality. Rare complications include: distal urethral necrosis, bladder injury, urethral injury, ureteric injury, and vaginal scarring or narrowing with consequent dyspareunia [815].

One case series reported a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticula within one year [781], Ingber *et al*., found a 10.7% recurrence rate in 122 women undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [814] or radiation. Recurrent urethral diverticulum following initial successful urethral diverticulectomy may occur as a result of a new infection or traumatic insult such as childbirth, a new urethral diverticulum, or recurrence of the original lesion. Recurrence of urethral diverticulum may be due to incomplete removal of the urethral diverticulum, inadequate closure of the urethra, residual dead space (circumferential diverticula), or other technical factors. Repeat urethral diverticulectomy represents a unique challenge due to altered anatomy, scarring, and difficulty identifying proper anatomical planes.

Stress urinary incontinence can be worsened or occur *de novo* after diverticulectomy. This is most likely due to sphincteric damage from the dissection or scarification preventing urethral closure. *De novo* SUI (10.6% of women) seems to be more common in proximal and large (> 30 mm) diverticula [794]. However, Lee *et al*., noted at least some *de novo* SUI in 49% of patients following urethral diverticulectomy; most of which was minor and did not require additional therapy [816]. Only 10% of these individuals underwent subsequent SUI surgery. Treatment for SUI after diverticulectomy is not well described in the literature. The most commonly reported operation is an autologous pubovaginal sling [805] followed by retropubic suspension [806]. However, there are two reported cases of synthetic mesh sling to treat SUI, without mesh complications [781, 794], but this is controversial.

4.9.4.3 Pathological findings

Most urethral diverticula are lined with squamous cells, urothelium or columnar epithelium [777, 817, 818]. In a meta-analysis, there was a high prevalence of chronic or acute inflammation (68.6%) and the most commonly reported lesions were nephrogenic metaplasia, which occurred in 8% of cases. Diverticula may undergo neoplastic alterations (6%), including invasive adenocarcinoma [819], followed by squamous cell carcinoma in 0.7%. It is unknown if the diverticulum forms first and then transforms into a malignancy or if the malignancy develops first. These malignancies are treated in a similar fashion to urethral cancer in women.

4.9.5 *Summary of evidence and recommendations for urethral diverticulum*

Summary of evidence	LE
Magnetic resonance imaging has the best sensitivity and specificity for the diagnosis of urethral diverticulum.	3
Surgical removal of symptomatic urethral diverticulum provides good long-term results; however, women should be counselled of the risk of recurrence and *de novo* SUI.	3

Recommendations	Strength rating
Offer surgical removal of symptomatic urethral diverticulum.	Weak
If conservative treatment is adopted, warn patients of the small (1–6%) risk of cancer developing within the diverticulum.	Weak
Carefully question and investigate patients for coexisting voiding dysfunction and urinary incontinence (UI).	Strong
Following appropriate counselling, address bothersome stress urinary incontinence at the time of urethral diverticulectomy with concomitant non-synthetic sling.	Weak
Counsel patients regarding the possibility of *de novo* or persistent LUTS including UI, despite technically successful urethral diverticulectomy.	Strong

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6. CONFLICT OF INTEREST

All members of the Non-neurogenic Female LUTS Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/non-neurogenic-female-luts/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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1. INTRODUCTION

Lower urinary tract symptoms (LUTS) encompass storage, voiding and post-micturition symptoms [1]. Storage symptoms include frequency, urgency, nocturia and urinary incontinence (UI) (stress UI [SUI], urgency UI [UUI] and mixed UI [MUI]). Voiding symptoms include hesitancy, intermittency, slow stream, straining, splitting or spraying of the urinary stream and terminal dribble. Post-micturition symptoms include post-void dribbling and feeling of incomplete bladder emptying. Lower urinary tract symptoms are often broadly classified into clinical syndromes/entities such as overactive bladder (OAB), underactive bladder (UAB), UI, nocturia, dysfunctional voiding, or genito-urinary fistulae.

LUTS are common in women [2-5] and cause a great deal of distress and embarrassment [6], as well as significant costs to both individuals and society [7]. Estimates of prevalence vary according to the definition and population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost [7].

1.1 Aim and objectives

These Guidelines from the European Association of Urology (EAU) Working Panel on Non-neurogenic Female LUTS are written by a multidisciplinary group, primarily for urologists, but are likely to be referred to by other professional groups. The guidelines aim to provide sensible and practical evidence-based guidance on the clinical problems associated with female LUTS rather than an exhaustive narrative review. Such reviews for UI and other LUT syndromes are already available from the International Consultation on Incontinence [8] and other sources. Therefore, these EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of LUTS/UI in detail. The focus of these guidelines is on assessment and treatment, reflecting clinical practice, and they do not consider women with LUTS caused by neurological disease, or LUTS occurring in children, as these are covered by complementary EAU Guidelines [9, 10].

The current guidelines provide:

- A clear description of the assessment and treatment of common clinical problems. This can provide the basis for both individual patient management and for planning and designing clinical services.
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources.
- Clear guidance in those areas of practice for which there is little or no high-quality evidence.

The latest edition of the guideline has seen a significant expansion of scope from UI to non-neurogenic female LUTS. The primary consideration here is to include the significant population of women with functional urological conditions not necessarily associated with UI that were hitherto not accounted for in previous guidelines. Secondary considerations are to align more cohesively with the existing Non-neurogenic Male LUTS Guidelines. As a consequence of the anatomical and physiological differences between the male and female LUT, the prevalence, pathophysiology, diagnostic approach and management of male and female LUTS differ widely. For that reason, the EAU Guidelines Office decided to provide gender-specific guidelines on LUTS and UI.

1.2 Panel composition

The EAU Non-neurogenic Female LUTS Panel consists of a multidisciplinary group of experts, including urologists, a uro-gynaecologist, a urodynamic scientist, physiotherapists, a nurse practitioner continence care and patient advocates. All experts involved in the production of this document have submitted potential conflict of interest statements that can be viewed on the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions that require consideration together with the full-text versions. All documents are accessible through the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

1.4 Publication history

The first EAU Urinary Incontinence Guidelines were published in 2001. The guidelines have been modified since to broaden its scope specifically to include other female LUTS as of 2021. Except for pelvic organ prolapse, all other sections of the 2022 Female LUTS Guidelines have been fully updated.

2. METHODS

2.1 Introduction

For the 2021 Non-neurogenic Female Lower Urinary Tract Symptoms Guidelines, the existing text of the 2018 Urinary Incontinence Guidelines was restructured and expanded. The Patient/Population, Intervention, Comparison and Outcome (PICO) question-based format of the text was modified to improve readability, although the underlying PICO structure still informs search strategies.

For the 2022 Non-neurogenic Female Lower Urinary Tract Symproms Guidelines, databases searched included Medline, Embase, and the Cochrane Libraries, covering a time frame between 12 June 2020 and 07 September 2021 with a focus on high-level evidence only (systematic reviews and meta-analyses). A total of 187 unique records were identified, retrieved and screened for relevance. Detailed search strategies are available online: https://uroweb.org/guideline/non-neurogenic-female-luts/?type=appendices-publications.

For the 2022 edition of the guidelines a *de novo* systematic review (SR) was undertaken by the Panel on the subject of overactive bladder syndrome [11]. Full publication of the SR results are pending; however, the preliminary results have informed the corresponding sections of this guidelines update.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [12, 13]. Each strength rating form addresses a number of key elements, namely:

1. overall quality of the evidence which exists for the recommendation; references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [14];
2. magnitude of the effect (individual or combined effects);
3. certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. balance between desirable and undesirable outcomes;
5. impact of patient values and preferences on the intervention;
6. certainty of those patient values and preferences.

These key elements are the basis that panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words strong or weak [15]. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The guidelines were extensively peer reviewed prior to publication in 2021.

2.3 Future goals

- Systematic review of pelvic organ prolapse;
- Systematic review of synthetic/mesh-related mid-urethral sling complications;
- Systematic review of the diagnosis and treatment of UAB in women.

3. DIAGNOSIS

3.1 History and physical examination

Taking a thorough clinical history is fundamental to the process of clinical evaluation. Despite the lack of high-level evidence to support taking a history, there is universal agreement that it should be the first step in the assessment of anyone with LUTS. The history should include a full evaluation of LUTS, as well as sexual, gastrointestinal and neurological symptoms. Details of urgency episodes, the type, timing and severity of UI, and some attempt to quantify symptoms should also be made. The history should help to categorise LUTS as storage, voiding and post-micturition symptoms, and classify UI as SUI, UUI, MUI or overflow incontinence; the

latter being defined as “the complaint of UI in the symptomatic presence of an excessively (over-) full bladder (no cause identified)” [16].

The history should also identify patients who need referral to an appropriate clinic/specialist. These may include patients with associated pain, haematuria, history of recurrent urinary tract infection (UTI), pelvic surgery or radiotherapy, constant leakage suggesting a fistula (see Section 4.8), new-onset enuresis or suspected neurological disease. A neurological, obstetric and gynaecological history may help to understand the underlying cause and identify factors that may affect treatment decisions. Guidance on history-taking and diagnosis in relation to UTIs, neuro-urological conditions and chronic pelvic pain (CPP) can be found in the relevant EAU Guidelines [9, 17, 18]. Patients should also be asked about other comorbidity as well as smoking status, previous surgical procedures and current medications, as these may affect LUTS.

There is little evidence from clinical trials that carrying out a clinical examination improves outcomes, but widespread consensus suggests that clinical examination remains an essential part of assessment of patients with LUTS. Examination should include abdominal examination, to detect an enlarged urinary bladder or other abdominal mass, and digital examination of the vagina and/or rectum. Pelvic examination in women includes assessment of oestrogen status, pelvic floor muscle (PFM) function and careful assessment of any associated pelvic organ prolapse (POP). A cough stress test is necessary to look for SUI. Among women with genital prolapse, the cough test was found to show good agreement with urodynamic studies (UDS) in the detection of SUI [19]. Urethral mobility can be assessed. Pelvic floor muscle contraction strength can also be assessed digitally. A focused neuro-urological examination should also be routinely undertaken.

3.1.1 Summary of evidence and recommendation for history taking and physical examination

Summary of evidence	LE
History taking including symptoms and comorbidity and focused physical examination are essential parts of the evaluation of women with LUTS.	4

Recommendation	Strength rating
Take a complete medical history including symptoms and comorbidity and perform a focused physical examination for evaluation of women with LUTS.	Strong

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires/scales/indices, patient-reported outcome measures (PROMs) and health-related quality of life (QoL) measures. The latter include generic or condition-specific measures. Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, should have been shown to be sensitive to change. The US Food and Drug Administration (FDA) published guidance for industry on PROM instruments (questionnaires) in 2009 [20].

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies included mixed populations (men and women). This limits the extent to which results and conclusions from these studies can be applied to particular LUT syndromes in women. Some questionnaires (ICIQ-FLUTS, QUID, 3IQ, ICIQ-SF) have potential to discriminate UI types in women [21-23]. Others have been developed to measure symptoms and bother in OAB (OABQ-SF, B-SAQ) and other specific conditions. A newly developed patient assessment tool, the OAB- Bladder Assessment Tool (OAB-BAT), was found to be a valid and reliable OAB PROM that includes symptoms, bother, impacts and satisfaction with treatment [24]. A systematic review (SR) included 22 studies that assessed eleven case-finding tools for OAB. All tools were found to have good sensitivity and specificity for OAB or incontinence symptoms. The B-SAQ was the only tool in this SR to include screening for “red- flag” symptoms such as haematuria and pain, and it has also been validated in a primary care setting [25]. Some questionnaires are responsive to change and may be used to measure outcomes, although evidence for this is inconsistent [26, 27].

A SR including 73 studies assessed 27 specific and six generic instruments that measure QoL in women with UI. In this review, IQoL was found to be the most psychometrically robust disease-specific tool for use in English-speaking women with UI. It had the highest level of evidence for sufficient internal consistency, test-retest reliability, measurement error and hypothesis testing for construct validity. It is also the most translated instrument. Evidence on the performance of generic QoL tools for this population is limited [28]. There is no evidence to indicate whether use of QoL or condition-specific questionnaires has an impact on outcome of treatment.

Detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of these guidelines. For more information, we recommend the 6th International Consultation on Incontinence review on PRO assessment [29]. To date, there is not one questionnaire that fulfils all requirements for assessment of women with LUTS. Clinicians must evaluate the tools that exist, for use alone or in combination, for assessment and monitoring of treatment outcome [30]. The questionnaires can be found on the following websites: www.iciq.net, https://eprovide.mapi-trust.org, www.pfizerpcoa.com, www.ncbi.nlm.nih.gov.

3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	LE
Validated condition-specific symptom scores assist in the screening for and categorisation of LUTS.	3
Validated symptom scores measure the severity of UI and LUTS.	3
Both condition-specific and general health status questionnaires measure current health status and change following treatment.	3
Patient questionnaires cannot replace a detailed patient consultation and should only be used as part of a complete medical history.	4

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised initial assessment and follow-up of female LUTS.	Strong

3.3 Bladder diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of LUT dysfunction. Bladder diaries are a semi-objective method of quantifying symptoms, such as frequency of UI events, number of nocturia episodes, etc. They also quantify urodynamic variables, such as voided volume, 24-hour urine volume or nocturnal total urine volume.

Discrepancy between diary recordings and the patient rating of symptoms, e.g., frequency of UI, can be useful for patient counselling. Fluid intake and voided volume measurement can be used to support diagnoses and management planning, for example in OAB, and for identifying 24-hour or nocturnal polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a bladder diary is unlikely to accurately report 24-hour urine output.

Consensus terminology is now well-defined and widely accepted [1, 31]. However, the terms micturition diary, frequency/volume chart, bladder diary and voiding diary, have been used interchangeably for many years, but only bladder diaries include information on fluid intake, times of voiding, voided volumes, UI episodes, pad usage, degree of urgency and severity of UI recorded for at least 24 hours. When reviewing the evidence, all synonymous search terms have been included.

Two studies have demonstrated the reproducibility of diaries in both men and women [32, 33]. Another two studies have shown the feasibility, reliability and validity of the bladder diary [34, 35]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded by uroflowmetry [36, 37]. Another study found that keeping a bladder diary had a therapeutic benefit [38].

A number of observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [39-42]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance [43, 44]. Diary durations between three and seven days are routinely reported in the literature.

3.3.1 Summary of evidence and recommendations for bladder diaries

Summary of evidence	LE
Bladder diaries of 3–7-days duration are reliable tools for objective measurement of mean voided volume, day- and night-time frequency, and UI episode frequency.	2b
Bladder diaries are sensitive to change and are a reliable outcome measure.	2b

Recommendations	Strength rating
Ask patients with LUTS to complete a bladder diary as part of the standardised assessment of female LUTS.	Strong
Use a bladder diary with a duration of ≥ 3 days.	Strong

3.4 Urinalysis and urinary tract infection

Reagent strip (dipstick) urinalysis may indicate proteinuria, haematuria or glycosuria, or suggest UTI requiring further assessment. Please refer to the Urological Infections Guidelines for diagnosis and treatment of UTI [17].

Urine dipstick testing is a useful adjunct to clinical evaluation in patients in whom urinary symptoms are suspected to be due to UTI. Urinalysis negative for nitrite and leukocyte esterase may exclude bacteriuria in women with LUTS [45], and should be included, with urine culture when necessary, in the evaluation of all patients with LUTS. Urinary incontinence or worsening of LUTS may occur during UTI [46] and existing UI may worsen [47]. The rate and severity of UI were unchanged after eradication of asymptomatic bacteriuria in nursing home residents [48].

3.4.1 Summary of evidence and recommendations for urinalysis

Summary of evidence	LE
Urinalysis negative for nitrite and leukocyte esterase may exclude bacteriuria in women with LUTS.	3
UI may be a symptom during UTI, and LUTS may increase during UTI.	3
The presence of UTI worsens existing symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	Strength rating
Perform urinalysis as a part of the initial assessment of patients with LUTS.	Strong
If UTI is present with LUTS, reassess the patient after treatment.	Strong
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve UI.	Strong

3.5 Post-void residual volume

Post-void residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It is a measure of voiding efficiency, and results from a number of contributing factors. The detection of significant PVR volume is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract (UUT) dilatation and renal insufficiency. Both BOO and/or detrusor underactivity (DU) can potentially contribute to the development of significant PVR volume. Post-void residual volume can be measured by catheterisation or ultrasound (US).

Most studies investigating PVR volume have assessed mixed populations including those with neurogenic UI. In general, the data on PVR volume can be applied with caution to women with non-neurogenic LUTS. The results of studies investigating the best method of measuring PVR volume [48-53] have led to the consensus that US measurement of PVR volume is preferable to catheterisation due to its favourable risk–benefit profile.

The prevalence of significant PVR volume among patients with LUTS is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. In peri- and postmenopausal women without significant LUTS or pelvic organ symptoms, 95% had a PVR volume < 100 mL [54]. In women with UUI, PVR volume > 100 mL was found in only 10% of cases [55]. Other research has found that a high PVR volume is associated with POP, voiding symptoms and an absence of SUI [54, 56-58]. In women with SUI, the mean PVR volume was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having PVR volume > 100 mL [59]. Some authors have suggested that it is reasonable to consider a PVR volume > 100 mL to be significant, although many women may remain asymptomatic and hence it is imperative to consider the clinical context [55]. There is no consensus on what constitutes a significant PVR volume in women; therefore, the Panel suggests the additional use of bladder volume efficiency (BVE). Bladder volume efficiency is the proportion of the total bladder volume that is voided by the patient. Bladder volume efficiency can be calculated as a percentage: BVE = voided volume (VV)/(VV+PVR) × 100. This may be a more reliable parameter to evaluate poor voiding [46].

3.5.1 *Summary of evidence and recommendations for post-void residual volume*

Summary of evidence	LE
LUTS are associated with a higher PVR volume compared to asymptomatic population groups.	2

Recommendations	Strength rating
Measure post-void residual (PVR) volume in patients with LUTS during initial assessment.	Strong
Use ultrasound to measure PVR volume.	Strong
Monitor PVR volume in patients receiving treatments that may cause or worsen voiding dysfunction.	Strong
Provide bladder volume efficiency as an additional parameter when measuring PVR volume.	Weak

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome or facilitate discussion during counselling. The simplest form of urodynamic evaluation is uroflowmetry. The maximum flow rate (Q_{max}), the volume voided and the shape of the curve in addition to the PVR volume (see above) are the most important aspects to be assessed [29]. The bladder should be sufficiently full because of the volume dependency of Q_{max} [60, 61]. A minimum voided volume of 150 mL is advised in men, but there is little evidence to suggest a volume threshold in women. It is relevant to ask the patient whether or not the voiding is representative.

Invasive urodynamic tests are sometimes performed prior to invasive treatment of LUTS. These tests include multichannel cystometry and pressure–flow studies, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry and Valsalva leak point pressure (VLPP). The International Continence Society (ICS) and the United Kingdom Continence Society (UKCS) provide standards to optimise urodynamic test performance and reporting [62, 63]. A characteristic of a good urodynamic study is that the patient's symptoms are replicated, recordings are checked for quality control, and results interpreted in the context of the clinical problem, remembering that there may be physiological variability within the same individual [62]. Non-invasive alternatives for measurement of detrusor pressure and BOO include transabdominal wall near-infrared spectroscopy and US detrusor wall thickness analysis, but as yet, these techniques have not been adopted into routine clinical practice [29].

Further condition-specific information regarding the role of urodynamic testing in OAB, SUI, BOO and UAB can be found in respective sections of these guidelines.

3.6.1 *Variability*

In common with most physiological tests there is variability in urodynamic results. This has consequences for the reproducibility, diagnostic accuracy and predictive value of urodynamic testing. It has been stated that, at least in the case of cystometry and pressure–flow studies, one set of measurements suffices, but only if the patient's symptoms have been replicated [62]. Contradictory findings have been reported in studies assessing same-session repeatability of cystometric and pressure–flow studies [64, 65]. There is also conflicting evidence about the reproducibility of maximum urethral closure pressure (MUCP) measurement [64, 65]. One method of recording MUCP cannot be compared meaningfully to another [65, 66]. Valsava leak point pressure measurement is not standardised and there is minimal evidence about its reproducibility. No studies on the reproducibility of ambulatory monitoring in non-neurological patients have been published [29].

3.6.2 *Diagnostic accuracy*

Clinical diagnosis and cystometric findings sometimes do not correlate [67, 68] and asymptomatic women may have abnormalities on urodynamic testing. As the urodynamic diagnosis is often taken as the benchmark in the assessment of LUT function, this implies that other tests of LUT function may be biased. The diagnostic accuracy of urethral pressure profilometry [69] and urethral retro-resistance pressure measurement in SUI is poor [29]. Valsava leak point pressure did not reliably assess UI severity in a cohort of women selected for surgical treatment of SUI [70]. Urethral pressure reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [71]. Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry does, but the clinical relevance of this is also uncertain [72, 73].

A pressure–flow study, that is, the simultaneous measurement of flow rate and detrusor pressure during voiding, can reveal whether a poor flow rate and PVR volume are due to BOO, poor bladder contraction

strength/detruser underactivity (DU), or a combination of both. Also, it may provide information on the degree of pelvic floor relaxation and thus diagnose dysfunctional voiding. Several proposals to define BOO in women have been made. These definitions are based on detrusor pressure, either $P_{det}Q_{max}$ or the maximum value $P_{det.max}$, and the Q_{max} value, either during the pressure–flow study or during uroflowmetry. These measures are sometimes combined with the findings during fluoroscopic imaging (see Section 4.5.4.8) [74, 75]. Unlike the situation in men, there is no widely accepted threshold for BOO diagnosis in women. Bladder contraction strength parameters are derived from detrusor pressure and flow rate during a pressure–flow study or from stop tests [75], but again, validation is poor. Although these parameters estimate the strength of the contraction, they ignore its speed and persistence (see Section 4.4.3.2) [76]. A video-urodynamic study can be useful to detect the site of obstructed voiding, which may be anatomical or functional [77]. Also, video-urodynamics may detect bladder diverticulum or gross reflux as a pressure-absorbing reservoir.

3.6.3 ***Predictive value***

Performing urodynamic evaluation is only useful if it leads to more effective clinical care and better outcomes. A Cochrane review of eight randomised controlled trials (RCTs) showed that use of urodynamic tests in women with UI increased the likelihood of prescribing drugs and did not increase the likelihood of undergoing surgery. However, there was no evidence that this influence on decision-making altered the clinical outcome of treatment [78]. Most RCTs addressed the utility of urodynamic tests on SUI only, including women with uncomplicated SUI. A meta-analysis including four RCTs comparing surgical outcomes in women with self-reported SUI (or stress-predominant MUI) who were investigated via urodynamics with women who had office evaluation only, found that there was no difference in cure and complication rates [79]. In contrast, a large retrospective multicentre study found that only 36% of patients were defined as uncomplicated according to the definitions used in large RCTs [80]. The urodynamic observations were not consistent with the pre-urodynamic diagnosis in 1276 out of 2053 patients (62.2%). Voiding dysfunctions were urodynamically diagnosed in 394 patients (19.2%) and planned surgery was cancelled or modified in 304 of 1582 patients (19.2%) in whom data were available, due to the urodynamic findings [81].

The predictive value of urethral function tests remains unclear. In observational studies, there was no consistent correlation between the results of these tests and subsequent success or failure of SUI surgery [40-42, 82]. The same was true in a secondary analysis of an RCT [83].

The presence of preoperative detrusor overactivity (DO) in women with stress-predominant MUI has been associated with postoperative UUI but did not predict overall treatment failure following mid-urethral sling (MUS) surgery or colpo-suspension [83]. The urodynamic diagnosis of DO had no predictive value for treatment response in studies on antimuscarinics, onabotulinumtoxinA and sacral nerve stimulation in patients with OAB symptoms [84, 85]. Augmentation cystoplasty aims to abolish DO, improve bladder compliance and increase functional bladder capacity but there is no evidence to guide whether or not preoperative urodynamics are predictive of outcome. Most clinicians would, however, consider preoperative urodynamics as essential prior to contemplating augmentation cystoplasty.

A pressure–flow study is capable of discriminating BOO from DU as a cause of voiding dysfunction. The predictive value of parameters derived from such a study for voiding dysfunction after a surgical procedure for SUI is however low. A low preoperative flow rate and a low detrusor voiding pressure have been shown to correlate with voiding dysfunction after a tension-free vaginal tape (TVT) and an autologous fascial sling procedure, respectively [86-88]. Bladder contraction strength parameters combining flow rate and detrusor pressure only poorly predicted voiding dysfunction after autologous fascial sling [89]. *Post hoc* analysis of two high-quality surgical trials of TVT, Burch colpo-suspension and autologous fascial sling showed that no preoperative urodynamic parameter predicted postoperative voiding dysfunction in a selected population of women with low preoperative PVR volume [90, 91].

The Panel recognises that it may be valuable to use urodynamic test results to select the optimum management strategy; however, there is inconsistent evidence regarding the predictive value of such tests. When urodynamics and clinical assessment (i.e., by history and examination) are in disagreement, there needs to be a careful re-evaluation of the clinical symptoms and investigation results to ensure that the diagnosis is correct before invasive treatments are contemplated. Expert opinion recognises urodynamic testing as the most comprehensive analysis of LUT function. The primary aim of urodynamics includes reproduction of the patient's symptoms. The information one obtains from urodynamics may be very valuable to discuss and manage expectation regarding invasive treatment.

3.6.4 Summary of evidence and recommendations for urodynamics

Summary of evidence	LE
Urodynamics provide comprehensive analysis of LUT function.	4
Most urodynamic parameters show variability within the same session and over time, and this may limit clinical interpretation.	3
Different techniques of measuring urethral function may have good test–retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.	3
There may be inconsistency between history and urodynamic results.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a
Preoperative urodynamics in women with uncomplicated, clinically demonstrable SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the results of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that preoperative DO is associated with surgical failure of MUS in women.	3
The presence of preoperative DO may be associated with persistence of urgency postoperatively in women undergoing surgery for SUI.	3

Recommendations	Strength rating
Adhere to good urodynamic practice standards as described by the International Continency Society when performing urodynamics in patients with LUTS.	Strong
Do not routinely carry out urodynamics when offering treatment for uncomplicated stress urinary incontinence.	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated overactive bladder symptoms.	Strong
Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of urinary incontinence as they are primarily tests of urethral function.	Strong

3.7 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, as well as provide an objective evidence of response to treatment.

The clinical utility of pad tests in woman with UI has been assessed in two SRs [92, 93]. A 1-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise, with variation according to activity level [94]. A pyridium pad test showed fair agreement with UDS in the detection of SUI among women with genital prolapse, particularly in identifying occult incontinence in up to 10% of prolapse patients [19]. A pyridium pad test involves patients taking pyridium 200 mg three times daily, for a day, recording if an orange stain is noted on the pad and qualifying the type of leakage associated with the staining as either stress or urgency.

A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated with the degree of provocation increased [95]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [92, 96, 97]. Pad tests are responsive to change following successful treatment [98]. Pad testing using a standardised bladder volume (50% of cystometric capacity) was suggested to allow for a more reliable assessment of UI in a small study of 25 women [99]. There is no evidence that one type of pad test is superior to another.

3.7.1 Summary of evidence and recommendations for pad testing

Summary of evidence	LE
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2

Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2
Pad tests can be a useful tool in the research setting and are an optional investigation in clinical practice.	4

Recommendations	Strength rating
When a pad test is performed, use a standardised duration and activity protocol.	Strong
Use a pad test when quantification of urinary incontinence is required, especially to assess response to treatment.	Weak

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause LUTS. In clinical practice, imaging is used to understand the relationship between anatomy and function. Ultrasound and magnetic resonance imaging (MRI) have largely replaced x-ray imaging in the evaluation of the pelvic floor. Ultrasound is sometimes preferred to MRI because of its ability to produce three-dimensional (3D) and 4D (dynamic) images at lower cost and wider availability.

There is no need for UUT imaging unless a high-pressure bladder, severe POP or chronic urinary retention is suspected or diagnosed, or abnormal renal function tests are observed. In cases of suspected UI caused by an UUT anomaly or uretero-vaginal fistula, UUT imaging (urography, computed tomography [CT]) may be indicated [100].

*3.8.1 **Ultrasound***

Ultrasonography of the LUT plays a role in the differential diagnosis of women with LUTS and in cases presenting with haematuria.

Ultrasonography has been used in the evaluation of UI and pelvic floor since the 1980s. Different imaging approaches, such as abdominal, transvaginal, transrectal, perineal and transurethral are described. The bladder neck and urethra are easily visible and measurements can be done at rest and during straining, coughing and pelvic floor contraction. The parameters assessed in the diagnosis of SUI, for example, include bladder neck mobility or descent, urethro-vesical angle and urethral rotation [101, 102]. Ultrasonography can be used to assess PFMs and their function. Contraction of PFM results in displacement of pelvic structures that can easily be imaged on US. Integrity of the levator ani muscle can be determined by 3D transperineal US. Ultrasound may also provide information on the anatomical changes of the LUT and pelvic floor associated with persistence of symptoms post-treatment [103]. The specific role of US is discussed in the condition-specific sections of these guidelines where applicable.

*3.8.2 **Detrusor wall thickness***

As OAB syndrome is linked to DO, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). Transvaginal US seems to be more accurate with less inter-observer variability than transabdominal and transperineal approaches [104]. Several cut-off points have been suggested, from 4.4 to 6.5 mm. Other studies are contradictory and did not find this correlation. No consensus exists as to the relationship between OAB and increased BWT/DWT [105], and there is no evidence that BWT/DWT imaging improves management of OAB. There is no widely accepted, standardised bladder volume for bladder wall thickness measurement.

In a retrospective study including 227 women with symptoms of voiding difficulty (hesitancy, intermittency and poor stream), 74 (32.6%) were diagnosed with voiding dysfunction on the basis of free uroflowmetry and residual urine. While controlling for the effect of DO, the relationships between DWT and different parameters of voiding function in pressure–flow studies and free uroflowmetry were examined. The results indicated that DWT was not associated with any urodynamic parameters that may indicate BOO [106].

*3.8.3 **Magnetic resonance imaging***

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [107]. However, there is a large variation in MRI interpretation between observers [108] and little evidence to support its clinical usefulness in the management of LUTS/UI. There is no conclusive evidence that MRI evaluation of POP is more clinically useful than vaginal examination. Studies have assessed the use of imaging to assess the mechanism of MUS insertion for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not of the bladder neck [109]. Following MUS, a wider gap between pubic symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [110].

3.8.3.1 Summary of evidence and recommendation for imaging

Summary of evidence	LE
There is no consistent evidence that routine urinary tract imaging is useful in the evaluation or management of LUTS.	3
There is no consistent evidence that BWT/DWT measurement is useful in the management of OAB.	3

Recommendation	Strength rating
Do not routinely carry out imaging of the upper urinary tract or lower urinary tract as part of the assessment of LUTS.	Strong

3.9 Urinary biomarkers and microbiome

Interest in the role of urinary biomarkers for the diagnosis of LUT dysfunction has increased in recent years. Nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), prostaglandin E2, adenosin triphosphate (ATP) and purinergic receptors (P2X) in bladder tissue have been studied as biomarkers for OAB. Serum beta natriuretic peptide (BNP), urinary 6-sulfatoxymelatonin and C-reactive protein (CRP), melatonin, vasopressin levels have been studied in relation to nocturia. For SUI, urinary IL 12-70, urinary NGF, N-telopeptide of type I collagen (NTx) and urinary microbiome have been studied. Currently, studies investigating urinary biomarkers are methodologically limited often due to failing to control for confounding variables and results are conflicting [111].

Another area of discovery is the role of urinary microbiome in identifying and differentiating various types of UI and other LUT disease in women. A SR described studies showing differences in the types and relative proportions of bacteria such as *Lactobacillus, Gardnerella, and Atopobium vaginae*, among women with different types of UI compared with healthy controls. Urinary microbiome has also been shown to differ depending on women's response to anticholinergic treatment response [112]. Further research is needed before the place of urine microbiome assessment in the clinical pathway for women with LUTS is fully defined.

Further information on the diagnostic efficacy of biomarkers in OAB can be found in section 4.1.3.3

3.9.1 ***Summary of evidence and recommendation for urinary biomarkers***

Summary of evidence	LE
There is insufficient evidence on the diagnostic accuracy and validity of urinary biomarkers for LUT disease in women.	3
Differences in the urinary microbiome have been found to be associated with different types of LUT dysfunction in women, including UI, and with different responses to treatment.	3

Recommendation	Strength rating
Do not routinely use urinary biomarkers or estimation of the urinary microbiome in the diagnosis and management of LUT disease in women.	Strong

4. DISEASE MANAGEMENT

4.1 Overactive bladder

4.1.1 ***Epidemiology, aetiology, pathophysiology***

Overactive bladder is defined by the ICS as "urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of UTI or other obvious pathology" [113].Overactive bladder is a chronic condition and can have debilitating effects on QoL. The hallmark urodynamic feature is DO, although this may not be demonstrated in a large proportion of OAB patients, which may partly be due to failure to reproduce symptoms during urodynamic assessment.

The EPidemiology of InContinence (EPIC) study was one of the largest population-based surveys of the prevalence of LUTS and OAB [114]. It was a cross-sectional telephone survey of adults aged > 18 years conducted in five countries, including Canada, Germany, Italy, Sweden and the UK. The study included > 19,000

participants and demonstrated an overall prevalence of OAB symptoms of 11.8% (10.8% in men and 12.8% in women). Other studies have reported prevalences of up to 30 to 40%, with rates generally increasing with age [5].

Various theories have been proposed to explain the pathophysiology of OAB, mainly relating to imbalances in inhibitory and excitatory neural pathways to the bladder and the urethra or sensitivity of bladder muscle receptors. However, no definite identifiable causes have been established.

*4.1.2 **Classification***

Overactive bladder is generally classified into wet and dry, based on the presence or absence of associated UI.

*4.1.3 **Diagnostic evaluation***

Evaluation of symptoms of OAB follows the general pathway of evaluation of women with LUTS.

4.1.3.1 Bladder diaries

Diaries are particularly helpful in establishing and quantifying symptoms of frequency, urgency and UI, and may be valuable in assessing change over time or response to treatment. Several observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [39-42]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance. Diary duration of three to seven days is routinely used in the literature.

4.1.3.2 Urodynamics

Urodynamics is essential in establishing the presence of DO, but its absence does not preclude diagnosis of OAB, which is based on symptoms alone.

A Cochrane review of seven RCTs showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery. However, there was no evidence that this influence on decision-making altered the clinical outcome of treatment [78]. A sub-analysis of an RCT comparing fesoterodine to placebo [85] showed that the urodynamic diagnosis of DO had no predictive value for treatment response.

4.1.3.3 Summary of evidence and recommendations regarding associated conditions

Summary of evidence	**LE**
Bladder diaries of three to seven days' duration may be helpful in quantifying symptoms of OAB, and assessing response to treatment.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a

Recommendations	**Strength rating**
Request that patients complete at least a three-day bladder diary at initial evaluation for overactive bladder (OAB).	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated OAB symptoms.	Strong

4.1.3.4 Urinary biomarkers

A SR and meta-analysis indicated that urinary NGF (standard mean difference [SMD]: 1.45; 95% confidence interval [CI]: 0.53-2.36), NGF/Cr ratio (SMD: 1.23; 95% CI: 0.67-1.78), BDNF/Cr ratio (SMD: 0.78; 95% CI: 0.006-1.50), and BDNF/Cr ratio (Risk ratio [RR]: 0.78; 95% CI: 0.006-1.50) were increased in female OAB patients compared to healthy controls, whereas no difference was found for the PGE2/Cr and ATP/Cr ratios [115]. The current data is inadequate to assess any other potential biomarkers, such as urinary malondialdehyde (UMDA), ATP, and cytokines, in the management of OAB in female patients. Further studies are needed to establish their potential as diagnostic and management tools in OAB women.

*4.1.4 **Disease management***

4.1.4.1 Conservative management

In clinical practice, it has long been the convention that non-surgical therapies are recommended first because they usually carry the lowest risk of harm. While this remains true for non-pharmacological conservative treatments [e.g., pelvic floor muscle training (PFMT)], increasing concerns regarding the adverse events of some pharmacological treatments used to treat LUTS (e.g., anticholinergic drugs), particularly regarding cognitive function, have emerged and patients should be fully counselled regarding this potential risk.

4.1.4.1.1 Addressing underlying disease

LUTS, especially in elderly patients, are associated with multiple comorbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease;
- general cognitive impairment;
- sleep disturbances, e.g., sleep apnoea;
- depression;
- metabolic syndrome.

It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently have more than one condition. However, if new treatment for any associated comorbidity has been linked (usually by the patient or carer) to a deteriration in LUTS then this should be reviewed by a health care practitioner (HCP).

One study involving middle-aged women with type 1 diabetes mellitus showed that 10% had UUI. The study showed no correlation between early intensive insulin treatment of type 1 diabetes mellitus vs. conventional insulin treatment and found no difference in the prevalence of UI in these patients later in their lives [113].

4.1.4.1.1.1 Summary of evidence and recommendation regarding associated conditions

Summary of evidence	**LE**
There is a lack of evidence that improving any associated comorbid condition improves OAB.	3

Recommendation	**Strength rating**
Review any new medication associated with the development or worsening of urinary incontinence.	Weak

4.1.4.1.2 Adjustment of other medication

Although LUTS are listed as adverse effects of many drugs, this mainly derives from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of LUTS as a primary outcome, or were powered to assess the occurrence of statistically significant LUTS or worsening rates against placebo. In most cases, it is therefore not possible to be sure that any drug causes OAB/LUTS.

A structured scoping review failed to identify any studies addressing whether adjustment of specific medications could alter existing symptoms of OAB.

4.1.4.1.2.1 Summary of evidence and recommendations for adjustment of non-LUTS medication

Summary of evidence	**LE**
There is little evidence that alteration of non-uroselective medications can cure or improve symptoms of OAB.	3

Recommendations	**Strength rating**
Take a history of current medication use from all patients with overactive bladder (OAB).	Strong
Review any new medication associated with the development or worsening of OAB symptoms.	Weak

4.1.4.1.3 Urinary containment

Urinary containment is important for people with OAB wet or UUI when active treatment does not cure the problem, is delayed, or when it is not available or not possible. Some individuals may prefer urinary containment rather than active treatment with its associated risks. Containment includes the use of absorbent pads, urinary catheters, external collection devices and intravaginal devices. Detailed literature summaries can be found in the current International Consultation on Urological Diseases (ICUD) monograph [8] and in a European Association of Urology Nurses guidance document [116].

A SR of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, while evidence that disposable pads were better than washable pads was inconsistent [117]. A series of three crossover RCTs examined performance of different pad designs for differing populations [118, 119]. For women with light UI, disposable insert pads (within washable pouch pants) were most effective. In adults with moderate/severe UI, disposable pull-up pants were more effective for women.

A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [120]. A SR of non-randomised studies found no differences in UTI outcome or UUT changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [121].

Catheter-related bladder discomfort may be significant in women. Anticholinergics have been proposed to prevent or reduce this issue, but most of the evidence comes from clinical trials in the postoperative period, and the results are controversial [122-125]. One retrospective study including 40 women (most of them neurogenic) with long-term bladder catheters found intravesical botulinum toxin injections helped to prevent bladder pain and discomfort and catheter bypass/leakage. Patients reported an improvement in QoL and a significant 83% reduction in urine leakage [126].

Clean intermittent self-catheterisation (CISC) is the most commonly used therapy to manage high PVR volume and urinary retention [116]. It reduces the risk of complications such as UTI, UUT deterioration, bladder stones and overflow UI etc. It has not yet been established whether the incidence of UTI, other complications and user satisfaction are affected by either sterile or clean intermittent catheterisation (IC), coated or uncoated catheters or by any other strategy [127]. The use of hydrophilic catheters may be associated with a lower rate of UTI, but further evidence is needed, as current data comes from neurogenic patients [128]. The average frequency of catheterisation is four to six times per day [129] and the catheter sizes most often used are 12–16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [129]. Frequency of catheterisation needs to be based on individual need and capability, to prevent chronic and repeated over-filling of the bladder [130]. Thorough counselling regarding techniques, frequency, equipment and adverse effects of CISC should be given to all potential patients in line with good medical practice.

For people using CISC, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [131]. However, a recent narrative review suggests that, in certain populations, single-use catheters may reduce urethral trauma and UTI [132]. A Cochrane review summarising five trials comparing bladder washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [133].

A further Cochrane review summarising eight trials of whether antibiotic prophylaxis was beneficial for adults using CISC or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [134]. A multicentre RCT from the UK reported that prophylaxis was well-tolerated but development of antibiotic resistance was a concern [135].

4.1.4.1.3.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	**LE**
Pads are effective in containing urine.	1b
Antibiotic prophylaxis may help reduce incidence of UTI in patients who self-catheterise or have an indwelling catheter, but at the cost of increasing antimicrobial resistance.	1a

Recommendations	**Strength rating**
Ensure that women with overactive bladder (OAB) and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of wet OAB, either for temporary symptom control or when other treatments are not planned.	Strong
Offer prophylactic antibiotics to patients with recurrent UTI who perform clean intermittent catheterisation, after discussion regarding the risk of increasing antimicrobial resistance.	Strong

4.1.4.1.4 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity, regulation of bowel habit and fluid intake. Modification of these factors may improve symptoms of OAB.

4.1.4.1.4.1 Caffeine intake

Many drinks contain caffeine, particularly coffee, tea and cola. Conflicting epidemiological evidence of urinary symptoms being aggravated by caffeine intake has focused on whether caffeine reduction improves LUTS [136, 137]. A scoping review of fourteen interventional and twelve observational studies reported that reduction in caffeine intake may reduce symptoms of urgency, but the certainty of evidence was low, with significant heterogeneity in study populations [138].

4.1.4.1.4.2 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with OAB to relieve symptoms. Any advice on fluid intake given by HCPs should be based on 24-hour fluid intake and urine output measurements as retrieved from the bladder diary. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that an abnormally low or high 24-hour urine output should be investigated. The few RCTs that have been published provide inconsistent evidence [139-141]. In most studies, the instructions for fluid intake were individualised and it was difficult to assess participant adherence. All available studies were in women. An RCT showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI [141]. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving anticholinergics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [142]. Patients should be warned of the potential consequences of fluid restriction such as worsening of constipation or development of UTI.

4.1.4.1.4.3 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for LUTS in many epidemiological studies [143, 144]. There is evidence that the prevalence of both UUI and SUI increases proportionately with body mass index [145]. However, the evidence base largely relates to obesity and SUI rather than UUI and OAB. Therefore, no definite inference can be drawn between obesity and the prevalence of OAB.

4.1.4.1.4.4 Smoking

Smoking cessation is a general public health measure and has been shown to be weakly associated with improving urgency, frequency and UI [146, 147]. The effect of smoking cessation on LUTS was described as uncertain in a health technology assessment review [148].

4.1.4.1.4.5 Summary of evidence and recommendations for lifestyle interventions

Summary of evidence	**LE**
Reduction of caffeine intake may reduce symptoms of frequency and urgency.	2
Addition of personalised fluid intake advice to pharmacotherapy provides no additional benefit in patients with OAB.	2
Reduction in fluid intake by 25% may help improve symptoms of OAB but not UI.	1b
Obesity is a risk factor for UI in women, but the relationship to other OAB symptoms remains unclear.	1b
There is weak evidence that smoking cessation improves symptoms of OAB.	3

Recommendations	**Strength rating**
Encourage overweight and obese adults with overactive bladder (OAB)/urinary incontinence to lose weight and maintain weight loss.	Strong
Advise adults with OAB that reducing caffeine intake may improve symptoms of urgency and frequency, but not incontinence.	Strong
Review type and amount of fluid intake in patients with OAB.	Weak
Provide smoking cessation strategies to patients with OAB who smoke.	Strong

4.1.4.1.5 Behavioural and physical therapies

Approaches include bladder training (BT) and PFMT. Almost always in clinical practice, these are introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package, especially for adherence to training.

A SR on cognitive components of behavioural therapies for OAB concluded that they were neither well described nor rationalized. Behavioural therapy that includes a cognitive component shows promise for OAB

treatment, but its relative importance has not been evaluated nor rigorously studied. Cognitive strategies include mental distraction (the most common), relaxation and mindfulness practices [149].

4.1.4.1.5.1 Prompted voiding and timed voiding

The term 'prompted voiding' implies that carers, rather than the patient, initiate the patient going to void with the aim of preventing or reducing UI. This applies largely to an assisted care setting. One SR (including nine RCTs), comparing prompted voiding in comparison to standard care, suggested evidence of short-term benefit for management of UI, but longer-term effects are unknown [150].

Timed voiding is defined as fixed, predetermined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs, finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [151].

4.1.4.1.5.2 Bladder training

Bladder training is a programme of patient education along with a scheduled voiding regimen with gradually increasing intervals. Specific goals are to correct faulty patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes and restore patient confidence in controlling bladder function. The ideal form or intensity of a BT programme for OAB/UI is unclear. It is also unclear whether or not BT can prevent development of OAB/UI.

There have been three SRs on the effect of BT compared to standard care confirming that BT is more effective than no treatment in improving UUI [67, 148, 152]. The addition of BT to anticholinergic therapy did not improve UUI compared to anticholinergics alone but it did improve frequency and nocturia [153]. A review identified seven RCTs in which BT was compared to drug therapy alone and only showed a benefit for oxybutynin for cure or improvement of UUI [153].

4.1.4.1.5.3 Pelvic floor muscle training

An immediate effect of PFM contraction is simultaneous inhibition of urgency, detrusor contraction and incontinence [154]. Intensive and regular strength training of the PFMs over time increases both PFM contraction strength and endurance, and changes the morphology of the pelvic floor, which may yield more effective inhibition of the detrusor and help to stabilize the proximal urethra and improve urethral function. There is a lack of basic and mechanistic studies to confirm that change in pelvic floor morphology improves OAB symptoms.

A SR of eleven RCTs [155] including women with OAB compared the efficacy of PFMT vs. inactive control, usual care, other lifestyle modification or other intervention. Pelvic floor muscle training significantly reduced OAB symptoms (frequency and UUI) in five RCTs, while the remaining six reported no significant difference. Significant heterogeneity in protocols precluded meaningful comparisons.

4.1.4.1.5.4 Electrical stimulation

The methods of delivery of electrical stimulation (ES) vary considerably. Electrical stimulation of the PFM can also be combined with other forms of conservative therapy; e.g., PFMT with and without biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their PFMs and in patients with OAB and UUI with the aim of inhibiting detrusor contraction. There is, however, a lack of basic and mechanistic studies to confirm this theory.

A SR of the effect of ES included 51 trials with 3,443 adults with OAB symptoms [156], with quality of evidence ranging from very low to moderate. Moderate-quality evidence suggests that ES is more likely to improve OAB symptoms compared to sham control, no treatment or placebo. Moderate-quality evidence suggests that ES is more likely to improve OAB symptoms compared to anticholinergic therapy. There is insufficient evidence for comparisons with PFMT and between different types of ES.

4.1.4.1.5.5 Acupuncture

A SR with meta-analysis of ten RCTs including 794 patients (590 women) reported that acupuncture might have an effect in reducing OAB symptoms compared to sham treatment [157]. The studies were of low quality and compared electro-acupuncture vs. sham acupuncture, or electro-acupuncture plus tolterodine vs. tolterodine alone. An up-to date SR from the Cochrane collaboration is planned for 2022 [158].

4.1.4.1.5.6 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2–S4 sacral plexus. Stimulation is percutaneous with a fine (34-G) needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS) that delivers

stimulation via surface electrodes that do not penetrate the skin. Treatment cycles typically consist of twelve weekly treatments of 30 minutes.

4.1.4.1.5.6.1 Percutaneous posterior tibial nerve stimulation

The reviewed studies included a SR, two twelve-week RCTs of P-PTNS compared with sham treatment [159-161], one comparing PTNS to tolterodine, and a three-year extension trial utilising a maintenance protocol in patients with UUI [162, 163]. The results of studies of PTNS in women with refractory UUI are consistent. These results suggest that PTNS improves UUI in women who do not have adequate improvement or cannot tolerate anti-muscarinic therapy. Improvements in voiding frequency, nocturia, urgency, incontinence episodes, cystometric capacity and compliance were described in the SR [161]. The major complication was pain at the puncture site, but the incidence was low. However, there was no good evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women.

4.1.4.1.5.6.2 Transcutaneous posterior tibial nerve stimulation

A small RCT compared T-PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [164]. Women in the T-TPNS group were more likely to achieve improvement at the end of therapy. A SR of thirteen trials (ten RCTs and three cohort studies) compared the efficacy of T-PTNS (duration four to twelve weeks) with sham treatment, anticholinergics, and exercise in treatment of adults with OAB symptoms [165]. Of note, the populations were adult women and men, and some studies included patients with neurogenic OAB. Meta-analysis was possible in two RCTs comparing T-PTNS with sham treatment, and revealed mean reduction in total international consultation on incontinence modular questionnaire (ICIQ) Urinary Incontinence Short Form (ICIQ-UI SF) associated with T-PTNS of –3.79 points.

A SR with meta-analysis including three RCTs (two RCTs comparing P-PTNS with solifenacin and one RCT comparing T-PTNS with oxybutynin) found PTNS to be more effective than anticholinergics in improving UUI in women with OAB on short-term follow-up of ≤ 12 weeks (mean difference [MD]: -0.67; 95% CI: -1.31 to -0.02). The certainity of evidence was low to moderate. However, the meta-analysis revealed no statistically significant difference between PTNS and anticholinergics in improvement of mean symptoms scores on validated questionnaires, frequency, or urgency episodes [11]. Adding anticholinergics to PTNS added no statistically significant value to improvement of any of OAB symptoms than PTNS alone [166].

A small RCT compared BT alone, BT plus P-PTNS and BT plus T-PTNS in women with idiopathic OAB. Both P-PTNS and T-PTNS were more effective than BT alone. These two tibial nerve stimulation methods had similar clinical efficacy but with slight differences: TTNS had shorter preparation time, less discomfort level and higher patient satisfaction than PTNS [166].

4.1.4.1.5.7 Summary of evidence and recommendations for behavioural and physical therapies

Summary of evidence	**LE**
Bladder training is effective for improvement of UUI in women.	1b
Combination of BT with anticholinergic drugs does not result in greater improvement of UUI, but may improve frequency and nocturia.	1b
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
Pelvic floor muscle training may improve symptoms of frequency and incontinence in women.	1b
Electrical stimulation may improve symptoms of OAB in some women, but the type and mode of delivery of ES remains variable and poorly standardised.	1a
Percutaneous-posterior tibial nerve stimulation appears effective in the short-term for improving UUI in women who have had no benefit from anticholinergic medication but in general is not curative.	2b
A maintenance programme of P-PTNS has been shown to be effective for up to 3 years.	1b
Percutaneous-PTNS has comparable effectiveness to tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
Transcutaneous-PTNS appears to be effective in reducing OAB symptoms compared to sham treatment.	1a

Recommendations	**Strength rating**
Offer prompted voiding for adults with overactive bladder (OAB) who are cognitively impaired.	Strong
Offer bladder training as first-line therapy to adults with OAB/UUI.	Strong
Ensure that pelvic floor muscle training programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for improvement of OAB/UUI in women who have not benefitted from anticholinergic medication.	Strong

4.1.4.2 Pharmacological management

4.1.4.2.1 Anticholinergic drugs

Anticholinergic (antimuscarinic) drugs are currently the mainstay of treatment for OAB. They differ in their pharmacological profiles, such as muscarinic receptor affinity and other modes of action and in their pharmacokinetic properties, such as lipid solubility and half-life.

The evaluation of cure or improvement of OAB is made harder by the lack of standard definitions. In general, a SR noted that the overall treatment effect of drugs is usually small but larger than that of placebo. Some RCTs have UI as an outcome rather than UUI. Dry mouth is the commonest adverse effect, although constipation, blurred vision, fatigue and cognitive dysfunction may occur with anticholinergic drugs [152].

Immediate-release (IR) anticholinergic preparations provide maximum dosage flexibility, including an off-label on-demand use. Immediate-release drugs have a greater risk of adverse effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system and gel developed for oxybutynin provide alternative formulations.

Seven SRs of individual anticholinergic drugs vs. placebo have been reviewed [152, 167-172]. Most studies included patients with a mean age of 55–60 years. The evidence reviewed was consistent, indicating that ER and IR formulations of anticholinergics offer clinically significant short-term improvement of OAB compared to placebo. On balance, IR formulations tend to be associated with more adverse effects compared to ER formulations [171].

A network meta-analysis of 128 RCTs comparing anticholinergics with placebo or other anticholinergics revealed that all anticholinergics, except imidafenacin, showed significant cure or improvement rates for OAB symptoms in both sexes [173].

Cure of UUI is deemed to be the most important outcome measure. Table 1 shows a summary of the findings from SRs [152]. Every drug for which cure of UUI was available showed superiority compared to placebo, but the absolute size of the effect was small. There is limited evidence that patients who do not respond to first-line anticholinergic treatment respond to a higher dose or a different anticholinergic agent [174, 175]. Risk of adverse events is often represented by trial withdrawal, although this does not reflect clinical practice. The cure rates for darifenacin were not included in the US Agency for Healthcare Research and Quality (AHRQ) review. Continence rates were 29–33% for darifenacin compared to 17–18% for placebo [152]. Transdermal oxybutynin showed a significant improvement compared with placebo and other oral formulations in the number of incontinence episodes and micturitions per day but cure of UI was not reported as an outcome [152].

Oxybutynin topical gel was superior to placebo for improvement of UUI, with a higher proportion of participants being cured [152, 176].

Table 1: Summary of cure and discontinuation rates of anticholinergic drugs from RCTs [152]

Drug	**No. of studies**	**No. of patients**	**RR (95% CI) (of curing UI)**	**NNT (95% CI) (to achieve one cure of UI)**
Cure of incontinence				
Fesoterodine	2	2465	1.3 (1.1–1.5)	8 (5–17)
Oxybutynin (includes IR)	4	992	1.7 (1.3–2.1)	9 (6–16)
Propiverine (includes IR)	2	691	1.4 (1.2–1.7)	6 (4–12)
Solifenacin	5	304	1.5 (1.4–1.6)	9 (6–17)
Tolterodine (includes IR)	4	3404	1.2 (1.1–1.4)	12 (8–25)
Trospium (includes IR)	4	2677	1.7 (1.5–2.0)	9 (7–12)
Discontinuation due to adverse events				
			RR (95% CI) (of discontinuation)	**NNT (95% CI) (for one discontinuation)**
Darifenacin	7	3138	1.2 (0.8–1.8)	
Fesoterodine	4	4433	2.0 (1.3–3.1)	33 (18–102)
Oxybutynin (includes IR)	5	1483	1.7 (1.1–2.5)	16 (8–86)
Propiverine (includes IR)	2	1401	2.6 (1.4–5)	29 (16–77)

Solifenacin	7	9080	1.3 (1.1–1.7)	78 (39–823)
Tolterodine (includes IR)	10	4466	1.0 (0.6–1.7)	
Trospium (includes IR)	6	3936	1.5 (1.1–1.9)	56 (30–228)

CI = confidence interval; IR = immediate release; NNT = number to treat; RR = relative risk; UI = urinary incontinence.

4.1.4.2.1.1 Comparison of different anticholinergic agents

Head-to-head comparison trials of the efficacy and adverse effects of different anticholinergic agents are of interest for decision-making.

A network meta-analysis revealed no clear best anticholinergic preparation for cure or improvement [173]. Darifenacin (40%), tolterodine IR and oxybutynin ER (13% each) appeared to score highest in indirect comparisons. Fesoterodine and oxybutynin IR were more effective than oxybutynin (transdermal) and tolterodine ER. There were no clinically significant differences between anticholinergics for voiding and UI outcomes.

Another network meta-analysis of 53 RCTs compared the efficacy and tolerability of solifenacin 5 mg with other oral anticholinergics in the treatment of adults with OAB symptoms [177]. Solifenacin 5 mg/day was significantly more effective than tolterodine 4 mg/day for reducing UUI episodes, but significantly less effective than solifenacin 10 mg/day for reducing micturition episodes. Solifenacin 5 mg/day showed significantly lower risk of dry mouth compared with other anticholinergics. There were no significant differences for the risk of blurred vision or constipation.

It is notable that nearly all the primary studies in this category were industry sponsored. Upward dose titration is often included in the protocol for the experimental arm but not for the comparator arm. In general, these studies have been designed to achieve regulatory approval. They have short treatment durations (twelve weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real-life practice is therefore debatable. Most trials were of low or moderate quality [169]. The 2012 AHRQ review included a specific section addressing comparisons of anticholinergic drugs (Table 1).

No single anticholinergic agent improved QoL more than another [169]. Dry mouth is the most prevalent adverse effect. Extended release formulations of short- and longer-acting drugs are associated with lower rates of dry mouth than IR preparations are [169, 178]. Oxybutynin IR shows higher rates of dry mouth than tolterodine IR and trospium IR show, but lower rates of dry mouth than darifenacin, 15 mg daily [169, 178]. Overall, oxybutynin ER causes higher rates of dry mouth than tolterodine ER does, although the incidence of moderate or severe dry mouth is similar. Transdermal oxybutynin has a lower rate of dry mouth than oxybutynin IR and tolterodine ER have, but an overall higher rate of withdrawal due to adverse skin reactions [169]. Solifenacin 10 mg daily has higher rates of dry mouth than tolterodine ER [169]. Fesoterodine 8 mg daily has a higher rate of dry mouth than tolterodine 4 mg daily [179-181]. Similar discontinuation rates have been observed, irrespective of differences in the occurrence of dry mouth.

4.1.4.2.1.2 Anticholinergic drugs versus conservative treatment

The choice of pharmacologic vs. conservative treatment of OAB patients is an important question. More than 100 RCTs and high-quality reviews are available [153, 169, 170, 182-184]. Most of these were independent studies. The main focus of the reviews was to compare the different drugs used to treat UUI. A U.S. health technology assessment [182] found that trials were of a low or moderate quality.

The combination of BT and solifenacin in female patients with OAB confers no additional benefit in terms of continence compared with solifenacin monotherapy [185]. A recent Cochrane review on the benefit of adding PFMT to other active treatments of UI in women showed insufficient evidence of any benefit in adding PFMT to drug treatment [186].

One RCT reported a similar improvement in subjective parameters with T-PTNS or oxybutynin [187]. One study compared tolterodine ER to transvaginal/anal ES in women with OAB symptoms and/or UUI without demonstrating any differences in UI outcomes [188].

A SR with meta-analysis included RCTs combining anticholinergics with various non-invasive modalities including pregabalin, topical estrogenic, and physiotherapy. The review showed that these combinations were associated with significantly higher improvement in mean symptoms score on validated questionnaires

(6 RCTs, MD: 0.55; 95% CI: 0.16-0.95), urgency episodes (4 RCTs, MD: 0.68; 95% CI: 0.04-1.32) and UUI episodes (5 RCTs, MD: 1.18; 95% CI 0.18-2.17). The quality of evidence was low to moderate [11].

A SR with meta-analysis of 57 RCTs assessed the role of placebo in patients with OAB, it showed that placebo had age-dependent statistically significant effect on improvement of OAB symptoms including urgency daily episodes (MD: -0.51; 95% CI: -0.60 to -0.43) and UUI episodes (MD: -0.05; 95% CI: -0.61 to -0.39) [189]. The authors concluded that placebo response is non-negligible and is of importance in RCTs as a control arm. The same group published a SR with meta-analysis of data retrieved from 57 RCTs on the nocebo effect of pharmacotherapy in patients with OAB (up to 80% females). They reported dry mouth as the most commen reported adverse event with mean rate of 4.9% (95% CI: 0.042 to -0.057) followed by constipation 2.6%, (95% CI: 0.022 to 0.031), the authors concluded that HCPs should appreciate the possible positive and negative patient expectation regarding pharmacotherapy for OAB in order to optimise the individual outcomes [190].

4.1.4.2.1.3 Anticholinergic drugs: adherence and persistence

Most studies on anticholinergic medication are short-term (twelve weeks). Adherence in clinical trials is considered to be higher than in clinical practice [191]. This topic has been reviewed for the development of a previous version of these guidelines [192]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at twelve months, and particularly high (68–95%) for oxybutynin. Two open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at two years of 49–84% [193, 194].

Five articles reported median days to discontinuation, but follow-up periods varied from < 30 up to 50 days [195-199]. In a military health system where free medication was provided, the median time to discontinuation extended to 273 days [196].

Data on adherence/persistence from open-label extension populations are questionable as it could be argued that these patients are self-selected on the basis of their compliance. A longitudinal disease analyser database study has indicated an increasing discontinuation rate, following treatment with anticholinergics, from 74.8% at one year to 87% at three years [200].

Several of the RCTs tried to identify the factors associated with low/lower adherence or persistence of anticholinergics. These were identified as:

- low level of efficacy (41.3%);
- adverse events (22.4%);
- cost (18.7%), although higher adherence rates were observed when drugs were provided at no cost to patients [196].

Other reasons for poor adherence included:

- immediate release formulations (lower persistence compared with ER formulations);
- age (lower persistence among younger adults);
- unrealistic expectations of treatment;
- gender distribution (better adherence/persistence in female patients);
- ethnic group (African–Americans and other ethnic minorities are more likely to discontinue or switch treatment).

4.1.4.2.1.4 Summary of evidence and recommendations for anticholinergic drugs

Summary of evidence	**LE**
No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI.	1a
Higher doses of anticholinergic drugs are more effective to improve OAB symptoms, but exhibit a higher risk of adverse effects.	1a
Once daily (ER) formulations are associated with lower rates of adverse events compared to IR preparations.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral anticholinergic drugs are, but has a high rate of withdrawal due to skin reactions.	1b
There is no consistent evidence to show superiority of drug therapy over conservative therapy for treatment of OAB.	1b
Behavioural treatment may have higher patient satisfaction rates than drug treatment.	1b
There is insufficient evidence as to the benefit of adding PFMT to drug treatment for OAB.	1b

Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2a
Most patients will stop anticholinergic agents within the first three months.	2a

Recommendations	**Strength rating**
Offer anticholineric drugs to woman with overactive bladder (OAB) who fail conservative treatment.	Strong
Consider extended release formulations of anticholinergic drugs whenever possible.	Strong
If an anticholinergic treatment proves ineffective, consider dose escalation, offering an alternative anticholinergic formulation, or the use of mirabegron (alone or in combination with an anticholinergic).	Strong
Encourage early review (of efficacy and adverse effects) of patients on anticholinergic medication for OAB.	Strong

4.1.4.2.2 Beta-3 agonists

Beta-3 adrenoceptors are the predominant beta receptors expressed on detrusor smooth muscle cells and their stimulation is thought to induce detrusor relaxation. Mirabegron was the first clinically available beta-3 agonist. Vibegron is another beta-3 agonist commercially available in some countries.

Mirabegron has undergone evaluation in industry-sponsored phase II and III trials [201-204]. Three SRs assessing the clinical effectiveness of mirabegron [201, 202, 205] reported that mirabegron at doses of 25, 50 and 100 mg results in significantly greater reduction in UI episodes, urgency episodes and micturition frequency than placebo, with no difference in the rate of common adverse events [202]. The dry rates in most of these trials are 35–40% for placebo and 43–50% for mirabegron. In all trials the significant differences were consistent only for improvement but not for cure of UI. Similar improvements in the frequency of UI episodes and micturition frequency were found whether or not patients had previously tried anticholinergic agents. One SR showed that mirabegron is as efficacious as most anticholinergics in reducing UUI episodes [206]. One SR [207] assessed the outcomes of mirabegron in women with OAB. It included seven RCTs, three non-RCTs and eleven observational studies. The review reported no statistical difference between mirabegron and anticholinergics in decreasing OAB symptoms on voiding diaries and symptom questionnaires on short-term follow-up (up to twelve weeks). However, at one year follow-up, there was statistically significant decrease in OAB symptoms (MD: -0.35; 95% CI: -0.51 to -0.19) in favour of mirabegron.

The most common adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to that with placebo [201, 204, 208].

A SR with meta-analysis of data pooled from three RCTs comparing vibegron (75 mg or 100 mg) with placebo in 2120 patients with OAB revealed significant improvement of urgency episodes (MD: -0.77; 95% CI: -1.03 to -0.52) and UUI episodes (MD: -0.45; 95% CI: -0.64 to -0.34) and mean voided volume (MD: 22.2; 95% CI: 17.36 to 27.7) associated with vibegron [209]. The review also reported that vibegron showed a favourable safety profile. Another SR that included three high-quality RCTs compared vibegron with anticholinergic monotherapy (imidacine and tolterodine) concluding similar efficacy in terms of improvements in mean number of micturitions, urgency and UUI episodes, but with less dry mouth in vibegron groups [210].

In a twelve-month, active-controlled RCT of mirabegron 50/100 mg vs. tolterodine ER 4 mg, improvement in efficacy at twelve weeks was sustained at twelve months in all groups. The reported dry rates at twelve months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [208]. *Post hoc* analyses of RCTs showed that clinical improvement in OAB severity translates into improvement in health-related quality of life (HRQoL), and efficacy is maintained in patients with more severe UI [211, 212]. No risk of QTc prolongation [213] and no raised intraocular pressure [214] were observed up to the 100 mg dose; however, patients with uncontrolled hypertension or cardiac arrhythmia were excluded from these trials. There is no significant difference in the rate of adverse effects at different doses of mirabegron [208]. Patients on concurrent medication (e.g., metoprolol) should be counselled that, due to common metabolic pathways, their drug dose may need to be adjusted. In the case of patients taking metoprolol, blood pressure should be monitored after starting mirabegron and, if necessary, the metoprolol dose may need to be changed.

Equivalent adherence was observed for tolterodine and mirabegron at twelve months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [208]. In mirabegron-treated patients, improvement in objective outcome measures correlates directly with clinically relevant

PROMs (Overactive Bladder questionnaire and Patient Perception of Bladder Condition) [211, 215]. Data from a large Canadian Private Drug Plan database suggest a higher adherence rate for mirabegron compared to anticholinergics [216].

An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg demonstrated that combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [217].

4.1.4.2.2.1 Summary of evidence and recommendation for beta-3 agonists.

Summary of evidence	LE
Mirabegron and vibegron are better than placebo and as efficacious as anticholinergics for improvement of OAB/UUI symptoms.	1a
Adverse event rates with mirabegron and vibegron are similar to those of placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron rather than dose escalation of solifenacin.	1b

Recommendation	Strength rating
Offer beta-3 agonists as an alternative to anticholinergics to women with OAB who fail conservative treatment.	Strong

4.1.4.2.3 Anticholinergics and beta-3 agonists: elderly patients and cognition

Trials have been conducted in elderly patients with OAB. Considerations in this patient group include the multifactorial aetiology of OAB, comorbidities such as cognitive impairment, the effect of concomitant medications, and the risk of adverse events. The effects of anticholinergic agents on cognition have been studied in more detail.

Systematic reviews have included sections on the efficacy and safety of anticholinergics in elderly patients [152, 169]. A 2012 SR found inconclusive evidence of the impact of anticholinergics on cognition [218].

Two recent longitudinal cohort studies in patients using anticholinergic drugs showed deterioration in cognitive function, alteration in central nervous system metabolism and an association with brain atrophy [219, 220]. As most of the study periods are short (four to twelve weeks), the long-term impact of anticholinergic agents specifically approved for OAB treatment on specific patient cohorts are poorly understood [221-224].

- *Oxybutynin:* There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [221, 223, 225, 226]. One RCT with oxybutynin topical gel focused on cognitive and psychomotor function after one week of treatment showed no clinically meaningful effect on recent memory or other cognitive functions in healthy elderly adults [226]. Another retrospective study did not show cognitive impairment after four weeks of treatment with transdermal oxybutynin [223]. Recent evidence has emerged from a prospective cohort study showing cumulative cognitive deterioration associated with prolonged use (mean follow-up 7.3 years) of anticholinergic medication including oxybutynin [219]. Another prospective cohort study including 376 nursing residents aged 65 and older taking oxybutynin and tolterodine showed a decline in activity of daily living after a median follow-up of 141 days, in spite of concomitant treatment with cholinesterase inhibitors [227].

- *Solifenacin:* One pooled analysis [228] showed that solifenacin did not increase cognitive impairment in elderly patients. No age-related differences in the pharmacokinetics of solifenacin in different age groups were found, although more frequent adverse events in patients aged > 80 years were observed. No cognitive effect on healthy elderly volunteers was shown [229]. In a sub-analysis of a large trial, solifenacin 5–10 mg improved symptoms and QoL in people aged ≥ 75 years who had not responded to tolterodine [230]. In patients with mild cognitive impairment, aged ≥ 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most adverse effects compared to oxybutynin IR [226, 231].

- *Tolterodine:* No change in efficacy or adverse effects related to age has been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [221]. Two RCTs in elderly patients found similar efficacy and adverse effect profile to those in younger patients [232-235].

Post hoc analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [236]. Duration of the RCTs was short (twelve weeks).

- *Darifenacin:* Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that, compared with placebo, darifenacin was effective with no risk of cognitive change, measured as memory scanning tests [237, 238]. Another study on darifenacin and oxybutynin ER in elderly people concluded that the two agents had similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [223].

- *Trospium chloride:* Trospium does not appear to cross the blood–brain barrier in healthy individuals due to its molecular characteristics (quaternary amine structure and hydrophilic properties). Two studies in healthy volunteers using electroencephalography showed no effect from trospium, while tolterodine caused occasional changes and oxybutynin caused consistent changes [239, 240]. No evidence as to the comparative efficacy and adverse effect profiles of trospium in different age groups are available. However, there is some evidence that trospium does not impair cognitive function in Alzheimer's disease patients if combined with cholinesterase inhibitors in a six month period [224], or in non-cognitively impaired patients over shorter periods (twelve weeks) [241] and that it is effective compared to placebo in the elderly [242].

- *Fesoterodine:* Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of 8 mg but not 4 mg dose in patients aged > 75 years [193]. Adherence was lower in patients aged > 75 years but effects on mental status were not reported [181, 193, 243]. A more recent RCT showed efficacy of fesoterodine in vulnerable elderly people with no differences in cognitive function at twelve weeks [244].

- *Mirabegron:* Analysis of pooled data from three RCTs showed efficacy and safety of mirabegron in elderly patients [245].

4.1.4.2.3.1 Applicability of evidence to the general elderly population

It is not clear how much the data from pooled and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of anticholinergic adverse effects may be the most helpful [246]. When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [247]. No consensus exists as to the best mental function test to detect changes in cognition [227, 248].

4.1.4.2.3.2 Anticholinergic burden

Several drugs have anticholinergic effects and, if another anticholinergic drugs are prescribed, possible cumulative effects on cognition should be considered. Lists of drugs with anticholinergic properties are available from several sources [249].

No studies were identified specifically in older people with LUTS, but evidence is available from observational cohort studies relating to the risk in a general population of older people.

Two SRs of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [250, 251]. Longitudinal studies in older people over two to four years have found increased rates of cognitive decline in patients on anticholinergics or drugs with anticholinergic effects [219, 220, 252, 253]. It is unclear whether there is a direct correlation between cognitive dysfunction caused by medication and the long-term risk of development of dementia.

4.1.4.2.3.3 Summary of evidence and additional recommendations for use of anticholinergic drugs in elderly patients

Summary of evidence	**LE**
Anticholinergic drugs are effective in elderly women suffering from OAB/UUI.	1b
Mirabegron has been shown to be efficacious and safe in elderly women suffering from OAB.	1b
In older women the cognitive impact of drugs with anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly women.	2
Darifenacin, fesoterodine, solifenacin and trospium have not been shown to cause cognitive dysfunction in elderly women in short-term studies.	1b

Recommendations	Strength rating
Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction.	Strong
Assess anticholinergic burden and associated comorbidity in women being considered for anticholinergic therapy for overactive bladder syndrome.	Weak

4.1.4.2.4 Oestrogens

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women. Available evidence is related mainly to SUI, and although some reviews include participants with UUI, it is difficult to generalise the results to women with predominantly OAB/UUI.

The association of LUTS with genitourinary syndrome of menopause (GSM) should be considered [254]. Genitourinary syndrome of menopause (GSM) is a new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina and LUT. These include mucosal pallor/erythema, loss of vaginal rugae, tissue fragility/fissures, vaginal petechiae, urethral mucosal prolapse, introital retraction and vaginal dryness. There is evidence from a SR to suggest benefit from vaginal oestrogen therapy in GSM [255]. All vaginal oestrogens demonstrated superiority in objective and subjective end points of GSM compared with placebo. Only some trials demonstrated superiority vs. placebo in urogenital symptoms (UI, recurrent UTI, urgency and frequency). No significant difference was observed between various doses and dosage forms of vaginal oestrogen products. Vaginal oestrogen showed superiority over vaginal lubricants and moisturisers for the improvement of objective clinical end points of vulvovaginal atrophy but not for subjective end points [255].

Available evidence suggests that vaginal treatment with oestradiol and oestriol is not associated with increased risk of thromboembolism, endometrial hypertrophy, and breast cancer that is seen with systemic administration [256-258].

4.1.4.2.4.1 Summary of evidence and recommendation for oestrogen therapy

Summary of evidence	LE
Vaginal oestrogen therapy may improve symptoms associated with GSM, of which OAB may be a component.	1a

Recommendation	Strength rating
Offer vaginal oestrogen therapy to women with LUTS and associated symptoms.	Weak

4.1.4.2.5 Placebo

Placebo has a clear effect on the improvement of OAB signs and symptoms, and the overall placebo responses in various outcomes studied are statistically significant and, for some of the outcomes, possibly clinically significant. A recent SR including 57 studies with 12901 patients showed a standardised MD of -0.45 (95% CI: -0.51 to -0.40; $p < 0.001$) for daily micturition episodes, -0.33 (95% CI: -0.42 to -0.24; $p < 0.001$) for daily nocturia episodes, -0.46 (95% CI: -0.55 to -0.37; $p < 0.001$) for UUI episodes, -0.50 (95% CI: -0.61 to -0.39; $p < 0.001$) for daily urgency episodes, -0.51 (95% CI: -0.60 to -0.43; $p < 0.001$) for daily incontinence episodes, and 0.25 (95% CI: 0.211–0.290; $p < 0.001$) for volume voided per micturition [189]. The placebo response seems to be non-negligible in OAB, supporting the requirement for placebo control in RCTs.

4.1.4.3 Surgical management

4.1.4.3.1 Bladder wall injection of botulinum toxin A

Onabotulinum toxin A (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both sexes [259, 260]. Surgeons should be aware that other doses of onabotA and other formulations of botulinumtoxin A, abobotulinumtoxin A and incobotulinumtoxin A, are not licensed for use in OAB/UUI. Doses for onabotA are not transposable to the other brands of botulinumtoxin A. The continued efficacy of repeat injections is usual, but discontinuation rates may be high [261, 262]. The most important adverse events related to onabotA 100U injection detected in the regulatory trials were UTI and an increase in PVR volume that may require CISC [263].

Following a dose-ranging study in which 100 U onabotA was established as the optimum dose, a phase III trial randomised (1:1) the same group of 557 OAB-wet patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline, the population had on average > 5 episodes of UUI, ~12 micturitions per day and a small PVR volume. At week twelve, in patients treated with onabotA, UUI episodes/day were halved and the number of micturitions/day reduced by > 2. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [263]. Rates of urinary retention were not reported in SRs, and a Cochrane review reported no significant difference in PVR volume between the onabotA and placebo groups [264].

Quality of life was substantially improved in the onabotA arm, as shown by the > 2.5 times improvement in Incontinence Quality of Life Questionaire (I-QOL) scores compared to baseline. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in elderly and frail elderly people [265], although the success rate might be lower and the PVR volume (> 150 ml) higher in this group.

The median time to request retreatment in the pooled analysis of the two RCTs was 24 weeks [260, 263]. Follow-up over 3.5 years showed consistent or increasing duration of effect for each subsequent treatment, with a median of 7.5 months. Considerable differences were noted in patient outcomes on secondary analysis [266].

An RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed similar rates of improvement in UUI over the course of 6 months [267]. However, patients receiving onabotA were not only more likely to have cure of UUI (27% vs. 13%), but also had higher rates of urinary retention during the initial 2 months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking anticholinergics were more likely to have dry mouth. These results are further strengthened by a 2017 SR and network meta-analysis including 65 RCTs of onabotulinum toxin A vs. oral therapies (anticholinergics and mirabegron) for OAB at twelve weeks [268]. This review reported that patients receiving onabotulinum toxinA had the greatest reduction in UUI episodes, urgency episodes, micturition frequency and the highest odds of achieving dryness, as well as ≥ 50% reduction from baseline UI episodes/day (type not specified). However, adverse events were not reported in this network meta-analysis.

Identification of DO in urodynamics does not appear to influence the outcome of onabotulinum toxin A injections in patients with UUI [269].

4.1.4.3.1.1 Summary of evidence and recommendations for bladder wall injection of botulinum toxin A

Summary of evidence	**LE**
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and improving QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy but discontinuation rates are high.	2a
There is a risk of increased PVR volume and UTI with onabotulinum toxin A injections.	2
The risk of bacteriuria after onabotulinum toxin A (100 U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A (100 U) is superior to anticholinergics and mirabegron for cure of UUI and improvement of symptoms of OAB at twelve weeks.	1a

Recommendations	**Strength rating**
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with OAB/UUI refractory to conservative therapy or drug treatment.	Strong
Warn patients of the limited duration of response, risk of UTI and possible prolonged need for clean intermittent self catheterisation prior to treatment with onabotulinum toxin A.	Strong

4.1.4.3.2 Sacral nerve stimulation

Sacral nerve stimulation involves placing electrodes adjacent to the sacral nerve roots and delivering an electric current to the area via an attached battery implanted in the buttock, which delivers low-amplitude stimulation resulting in modulation of neural activity and stabilisation of bladder electrical activity through a mechanism that is, as yet, not fully understood. In most centres, test stimulation with a temporary or permanent electrode is performed to assess response, before undertaking permanent stimulator implantation. Currently, the only

reliable predictor for treatment success in SNS is test stimulation. A SR did not find predictive factors of success due to low level of evidence of included studies (small, retrospective and heterogeneous populations) [270] .

All randomised studies suffer from the limitation that patients cannot be blinded to the treatment allocation since all recruited patients have to respond to a test phase before randomisation. A Cochrane review in March 2008 [271] identified three RCTs that investigated SNS in patients with refractory UUI. The majority of studies compared a strategy of immediate implantation with delayed implantation.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at six months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at six months compared with 1.6% of the control group [272]. The effect on QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions. The other RCT achieved similar results, although these patients had already been included in the first report [273].

The results of seventeen case series of patients with UUI, who were treated early with SNS, were reviewed [274]. After follow-up of one to three years, ~50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50–90% improvement, and 25% demonstrated < 50% improvement. Two case series describing the outcome of SNS, with a mean or median follow-up of ≥ 4 years [275, 276] reported continued success (> 50% improvement of original symptoms) in patients available for follow-up. Cure rates for UUI were 15% [276].

A more recent RCT comparing a strategy of onabotulinum toxin A injection (200 IU), repeated as required, against a strategy of test and, if indicated, subsequent permanent SNS, showed lower cure rates with SNS at six months: 20% in the onabotulinum toxin A group and 4% in the SNS group had complete resolution of UUI [277]. Forty-six per cent in the onabotulinum toxin A group and 26% in the SNS group had ≥ 75% reduction in the number of episodes of UUI [278]. Two-year follow-up data from 87% of participants in this trial suggest no significant differences in treatment outcomes over 2 years, although satisfaction rates and treatment endorsement remain higher with onabotulinum toxin. The rates of complete resolution of UI (5% for both) as well as ≥ 75% reduction in UUI episodes (22% onabotulinum toxin A vs. 21% SNS) were equivalent at the 2-year mark [279]. Sacral nerve stimulation revision and removal occurred in 3% and 9% of this cohort, respectively.

A 2018 review of studies including SNS with ≥ 6 months follow-up reported dry rates of 43–56% [280]. Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33–41% [276, 277]. In a sub-analysis of the RCT similar success rates were found in patients with or without urodynamic DO [281].

4.1.4.3.2.1 Summary of evidence and recommendation for sacral nerve stimulation

Summary of evidence	LE
Sacral nerve stimulation is more effective than continuation of failed conservative treatment for OAB/ UUI, but no sham controls have been used.	1b
Sacral nerve stimulation is similarly effective as onabotulinum toxin A 200 U injection at 24 months.	1b
In patients who have been implanted, 50% improvement of UUI is maintained in ≥ 50% of patients and 15% may remain cured at four years.	3
The use of tined, permanent, electrodes in a staged approach results in more patients receiving the final implant compared to those who have undergone temporary test stimulation.	4

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have overactive bladder/urge urinary incontinence refractory to anticholinergic therapy.	Strong

4.1.4.3.3 Laser treament

A recent SR evaluated the use of vaginal lasers in the treatment of OAB and evaluated short-term studies detailing minimal improvement [282]. In general the quality of reported studies were weak and long-term safety data were lacking. Before considering widespread use of laser for the treatment of SUI and OAB, additional good-quality studies with extended follow-up, systematic reporting of adverse events, and objective measures of outcomes (urodynamic, 24-hour pad test, voiding diaries) are required.

4.1.4.3.3.1 Summary of evidence and recommendation for laser treatment

Summary of evidence	LE
Vaginal laser therapy shows minimal OAB symptom improvement in the shortterm, with minimal complications, however, long-term efficacy and safety data are lacking.	3

Recommendation	Strength rating
Do not offer vaginal laser therapy to treat overactive bladder symptoms outside of a well regulated clinical research trial.	Strong

4.1.4.3.4 Cystoplasty/urinary diversion

4.1.4.3.4.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any segment can be utilised if it has the appropriate mesenteric length. Most of the evidence pertaining to cystoplasty comes from patients with neuropathic bladder dysfunction. One study did not find any difference between bivalving the bladder in the sagittal or coronal plane [283, 284]. The procedure can be done, with equal success by open or robotic techniques, although the latter takes more time [285].

There are no RCTs comparing bladder augmentation to other treatments for patients with OAB/UUI. Most often, bladder augmentation is used to correct neurogenic DO, small capacity or low-compliant bladders caused by fibrosis, chronic infection such as tuberculosis, radiation, or chronic inflammation from interstitial cystitis.

The largest case series of bladder augmentation in a mixed population of idiopathic and neurogenic UUI included 51 women [286]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. The results for idiopathic DO (58%) were less satisfactory than for neurogenic UUI (90%). Malignant transformation was not reported in this series; however, it has been documented in other series and a SR [287-289]. Fewer than 60 cases have been reported worldwide, and almost all are exclusively beyond 10 years after the original cystoplasty [290].

Adverse effects are common and have been summarised in a review with five to seventeen years follow-up of > 267 cases; 61 of which had non-neurogenic UUI [291]. Many patients may require CISC to obtain adequate bladder emptying (Table 2). It is unclear if mucolytic agents reduce mucus accumulation. The only RCT comparing various mucolytic agents did not find significant benefits with the use of N-acetylcysteine, aspirin, or ranitidine. In one small study (n = 40), subcutaneous octreotide immediately before, and for fifteen days after surgery yielded significant reductions in mucus production, the need for bladder irrigation to clear blockages, and mean duration of hospital stay [292]. Before cystoplasty, all potential complications should be outlined, and before and after surgery patients should be well supported by stoma/continence nurses.

Depending on the relative costs of onabotulinum toxin A and augmentation cystoplasty, the latter can be cost-effective within 5 years if the complication rate is low and duration of effect of onabotulinum toxin A is < 5 months [293].

Table 2: Complications of bladder augmentation

Short-term complications	Affected patients (%)
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4

Long-term complications	Affected patients (%)
CISC	38
UTI/bacteriuria	70% asymptomatic 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.1.4.3.4.2 Detrusor myectomy (bladder auto-augmentation)
Detrusor myectomy aims to increase bladder capacity and reduce storage pressure by incising or excising a portion of the detrusor muscle, to create a bladder mucosal bulge or pseudo-diverticulum. It was initially described as an alternative to bladder augmentation in children [294].

Two case series in adult patients with idiopathic and neurogenic bladder dysfunction demonstrated poor long-term results caused by fibrosis of the pseudo-diverticulum [295, 296]. This technique is rarely, if ever, used nowadays.

4.1.4.3.4.3 Urinary diversion
Urinary diversion remains a reconstructive option for patients with intractable UI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation. Patients may be offered irreversible urinary diversion surgery. Options include ileal conduit urinary diversion, orthotopic neobladder and heterotopic neobladder with Mitrofanoff continent catheterisable conduit. There is insufficient evidence to comment on which procedure leads to the most improved QoL.

A small study comparing ileal with colonic conduits concluded that there are no differences in the relative risks (RR) of UUT infection and uretero-intestinal stenosis. However, no studies that have specifically examined these techniques for treatment of intractable OAB/UUI [283]. Therefore, careful consideration of which operation is undertaken depends on thorough preoperative counselling, access to stoma/continence nurses, as well as patient factors to allow for fully informed patient choice.

4.1.4.3.4.4 Summary of evidence and recommendations for cystoplasty/urinary diversion

Summary of evidence	LE
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion specifically for treatment of idiopathic OAB.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term severe complications.	3
The need to perform CISC following augmentation cystoplasty is common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3
Detrusor myectomy is ineffective in adults with UUI.	3

Recommendations	Strength rating
Ensure patient counselling and lifelong support both prior to and after major surgery as a treatment for overactive bladder (OAB).	Strong
Offer augmentation cystoplasty to patients with OAB/UUI who have failed all other treatment options and have been warned about the possible small risk of malignancy.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of clean intermittent self-catheterisation (ensure they are willing and able to do so) and that they need life-long surveillance.	Strong
Do not offer detrusor myectomy as a treatment for UUI.	Weak
Only offer urinary diversion to patients who have failed less-invasive therapies for the treatment of OAB/UUI, who will accept a stoma and have been warned about the possible small risk of malignancy.	Weak

4.1.5 *Follow-up*

Follow-up for women with OAB is guided by the type of treatment instituted and local service capacity. Standardisation of follow-up pathways can therefore be difficult. Here, we provide recommendations based on best practice and standards from clinical trials.

4.1.5.1 *Recommendations for follow-up of patients with overactive bladder*

Recommendations	Strength rating
Offer early follow-up to women who have been commenced on anticholinergic or beta-3 agonist therapy.	Strong
Offer repeat injections of onabotulinum toxin A, as required, to women in whom it has been effective (refer to the manufacturer's guidance regarding the minimum timeframe for repeat injections).	Strong
Offer life-long surveillance to women who have a sacral nerve stimulation implant to monitor for lead displacement, malfunction and battery wear.	Strong
Offer cystoscopic surveillance to women with an augmentation cystoplasty due to the small risk of malignancy.	Weak

4.2 Stress urinary incontinence

4.2.1 *Epidemiology, aetiology, pathophysiology*

Stress urinary incontinence is defined as the involuntary loss of urine on effort or physical exertion, is a significant health problem worldwide with social and economic impact on women and society. It is estimated that the number of women in the USA with UI will have increased from 18.3 million in 2010 to 28.4 million in 2050 [297]. The prevalence of SUI appears to peak between 45 and 59 years of age [298].

Data regarding the association of UI with ethnicity are conflicting. In several studies, SUI is more common in white women than in women of African–American or Asian–American origin [299, 300]. Other factors positively associated with SUI include parity, obesity, previous hysterectomy or pelvic surgery, diabetes mellitus [301] and pulmonary disease [302]. Physical activity level is another important factor that is positively correlated with SUI severity [303].

Two common, often overlapping, mechanisms for SUI have been described: (1) urethral hypermobility resulting from loss of support of the bladder neck and urethra; and (2) weakness of the urinary sphincter itself (intrinsic sphincter deficiency), which can result from trauma, radiotherapy, previous pelvic or uro-gynaecological surgery, neurological disease or ageing.

The mechanism behind urethral hypermobility as a cause of SUI is based on the "vaginal hammock" hypothesis [304]. The endopelvic fascia, which is attached to the upper (abdominal) side of the PFMs, links the muscles to the vagina and represents the "hammock", which can compress the urethra during rest and activity. This compression, combined with intrinsic urethral sphincter pressure, supports and maintains the urethra in the correct and closed position, preventing involuntary loss of urine, despite any increases in intravesical pressure. Damage to the supporting tissues (particularly the arcus tendinous fasciae pelvis, the central part of the fascia) can result in urethral hypermobility. Consequently, rather than being compressed at times of increased intra-abdominal pressure, the urethra moves caudally, funnelling the bladder neck, and is no longer compressed, resulting in SUI [304, 305]. In general, almost all treatments are used for both subtypes of SUI, but in general most treatments are more successful in patients with some degree of urethral hypermobility than for isolated intrinsic weakness of the urinary sphincter [306].

4.2.2 *Classification*

Patients with SUI can be classified as uncomplicated and complicated [307]. The Panel has reached a consensus on the definition to be used throughout this guideline document:

- Women with uncomplicated SUI: no prior surgery for SUI, extensive pelvic surgery, or pelvic radiotherapy; no neurogenic LUT dysfunction; no bothersome genito-urinary prolapse; absence of voiding symptoms; and no medical conditions that affect the LUT. In cases where additional significant storage symptoms, especially OAB, are present, consider a possible diagnosis of MUI (see Section 4.3).
- Women with complicated SUI: previous surgery for incontinence or extensive pelvic surgery; history of pelvic irradiation; presence of anterior or apical POP; presence of voiding symptoms or neurogenic LUT dysfunction; and significant OAB/UUI. Neurogenic LUT dysfunction is reviewed in the EAU Guidelines on Neuro-Urology and will not be considered further in these guidelines [9]. The treatment of LUTS associated with genitourinary prolapse has been included in these guidelines (see Section 4.7).

4.2.3 ***Diagnostic evaluation***

4.2.3.1 *History and physical examination*

There is universal agreement that taking a history should be the first step in the assessment of anyone with UI. When the history categorises UI as probable SUI the presence of complicated or uncomplicated SUI can also be determined. Those patients who require rapid referral to an appropriate specialist can also often be identified from the clinical history.

There is little evidence from clinical trials that carrying out a clinical examination improves clinical outcomes, but there is widespread consensus that it remains an essential part of the assessment of women with SUI. It should include abdominal examination, vaginal examination and careful assessment of any associated POP, examination of the perineum and evaluation of PFM strength, as well as a neuro-urological examination. An attempt to reproduce the SUI should be made. A standing cough test has greater sensitivity for diagnosis of SUI compared with a supine cough test [308]. Despite this, the ICS has proposed a standardisation of the female cough stress test that includes a supine/lithotomy position with 200–400 mL fluid in the bladder and one to four coughs [309].

4.2.3.1.1 Summary of evidence and recommendation for history and physical examination

Summary of evidence	**LE**
A standing cough stress test is more sensitive than a supine test.	1b

Recommendation	**Strength rating**
Take a full clinical history and perform a thorough physical examination in all women presenting with stress urinary incontinence.	Strong

4.2.3.2 *Patient questionnaires*

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies did not include homogeneous populations of adult women diagnosed with SUI. This limits the extent to which results and conclusions from these studies can be specifically applied to women with SUI. Some questionnaires are used for prevalence studies; others are responsive to change and may be used to measure outcomes, although evidence on their sensitivity is inconsistent [26, 27]. There is no evidence to indicate whether use of QoL or condition-specific questionnaires has an impact on treatment outcome. To date, there is no one questionnaire that fulfils all requirements for the assessment of women with SUI.

4.2.3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	**LE**
Validated condition-specific symptom scores assist in the screening for and categorisation of UI.	3
Validated symptom scores measure the severity and troublesomeness of SUI.	3
Both condition-specific and general health status questionnaires measure current health status, and are responsive to change following treatment.	3

Recommendation	**Strength rating**
Use a validated and appropriate questionnaire as part of the standardised assessment of patients with stress urinary incontinence.	Strong

4.2.3.3 *Post-void residual volume*

It is important to evaluate PVR volume in patients with SUI; particularly in those who also have voiding symptoms or POP. The prevalence of a significant PVR volume in patients with SUI is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. Most studies investigating PVR volume have not included patients with SUI. In general, the data on PVR volume can only be applied with caution to adults with non-neurogenic SUI. In a cohort study of > 900 women with SUI, there was good correlation between PVR volume estimated by US and measured by catheterisation. The mean PVR volume was 39 mL measured by catheterisation and 63 mL estimated by US, with only 16% of women having PVR > 100 mL [59].

4.2.3.3.1 Summary of evidence and recommendations for post-void residual volume

Summary of evidence	LE
The majority of women with SUI do not have a significant PVR volume.	3
There is good correlation between PVR volume estimated using US and measured via catheterisation in women with SUI.	3

Recommendations	Strength rating
Measure post-void residual (PVR) volume, particularly when assessing patients with voiding symptoms or complicated stress urinary incontinence (SUI).	Strong
When measuring PVR volume, use ultrasound in preference to catheterisation.	Strong
Monitor PVR volume in patients scheduled for treatment that may cause or worsen voiding dysfunction, including surgery for stress urinary incontinence.	Strong

4.2.3.4 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, based on the assumption that it may help to provide or confirm diagnosis. The role of urodynamics in SUI evaluation remains poorly defined and is still under debate.

Invasive urodynamic tests are often performed prior to surgical treatment of SUI. Clinical diagnosis of incontinence and cystometric findings often do not correlate [67, 68]. The diagnostic accuracy of urethral pressure profilometry [69] and VLPP measurement in SUI is generally poor [310]. Measurement of MUCP correlates, albeit weakly, with incontinence severity [69], and there is conflicting evidence about its reproducibility [64, 65]. Methods of recording MUCP cannot be compared meaningfully [66]. Valsalva leak point pressures are not standardised and there is minimal evidence about reproducibility. Valsalva leak point pressure did not reliably assess incontinence severity in a cohort of women selected for surgical treatment of SUI [70]. The predictive value of the tests regarding treatment outcome remains unclear.

A Cochrane review including seven RCTs showed that urodynamic tests increased the likelihood of avoiding surgery for SUI. However, there is no evidence that this influence on decision-making alters the clinical outcome of treatment within trial populations [78].

A high-quality RCT (n = 630) compared office evaluation alone and combined with urodynamics in women with clinically demonstrable SUI about to undergo surgery. While urodynamics changed the clinical diagnosis in 56% of women [311], there was no difference in severity of SUI or any secondary outcome at twelve months' follow-up after SUI surgery [80]. A similar study also found that omission of urodynamics in the preoperative work-up of SUI did not lead to inferior results [312]. Patients in whom urodynamics were discordant with clinical assessment (n = 109) were randomly allocated to receive either immediate surgery or individually tailored therapy based on the urodynamic findings. In this trial, performing immediate surgery, irrespective of the result of urodynamics, did not result in inferior outcomes [313]. An RCT, in which 145 women were randomised to retropubic or trans-obturator MUS, concluded that when patients were stratified according to preoperative VLPP ($\leq$ or $>$ 60 cm H_2O), it was not linked to outcome after both synthetic MUS procedures [314].

Another study reported conflicting evidence. Valsalva leak point pressure or MUCP in the lowest quartile was predictive in terms of synthetic MUS failure at twelve months [83].

The Panel recognises that it may be valuable to use urodynamic test results to help select the optimum surgical procedure, but the evidence outlined above suggests that performing urodynamics in patients with uncomplicated SUI, which can be diagnosed based on detailed clinical history and demonstrated at examination, is not necessary. The role of urodynamics in complicated SUI is still under debate [315]. However, the Panel consensus is that urodynamics should be carefully considered in cases of SUI with associated storage symptoms; cases in which the type of incontinence is unclear; cases in which voiding dysfunction is suspected; and cases with associated POP or prior surgery for SUI. This is in line with other guideline documents in this area [67].

4.2.3.4.1 Summary of evidence and recommendations for urodynamics

Summary of evidence	LE
Preoperative urodynamic testing in women with uncomplicated, clinically demonstrable SUI does not improve surgical outcome for SUI.	1b
There is no consistent correlation between urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that preoperative DO is associated with surgical failure of MUS in women.	3

Recommendations	Strength rating
Do not routinely carry out urodynamic tests when offering treatment for uncomplicated stress urinary incontinence (SUI).	Strong
Perform preoperative urodynamic tests in cases of SUI with associated storage symptoms, cases in which the type of incontinence is unclear, cases in which voiding dysfunction is suspected, and cases with associated pelvic organ prolapse or prior surgery for SUI.	Weak
Perform urodynamic tests if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence as they are primarily tests of urethral function.	Strong

4.2.3.5 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of SUI, as well as a patient's response to treatment.

The clinical utility of pad tests for people with UI has been assessed in two SRs [92, 93]. A one-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g show good specificity but low sensitivity for diagnosis of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [94]. A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [95]. The usefulness of pad tests in quantifying severity and predicting treatment outcome is uncertain [92, 97]. Pad testing is responsive to change following successful treatment [98]. Pad testing using a standardised bladder volume (50% of cystometric capacity) has been suggested to allow for a more reliable assessment of UI in a small study of 25 women [99]. There is no evidence that one type of pad test is superior to another.

4.2.3.5.1 Summary of evidence and recommendations for pad testing

Summary of evidence	LE
A pad test can diagnose SUI accurately, but cannot determine the aetiology.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based pad testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on standardised pad tests can be used to measure treatment outcome.	2

Recommendations	Strength rating
Use a pad test of standardised duration and activity protocol.	Strong
Use a standardised pad test when quantification of stress urinary incontinence is required, especially to assess response to treatment.	Weak

4.2.3.6 Imaging

The role of imaging in SUI patients is limited. Many studies have evaluated imaging of bladder neck mobility by US and MRI, and concluded that SUI cannot be identified by a particular pattern of urethro-vesical movement [316]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with *de novo* SUI [317]. Studies have assessed the use of imaging to investigate the mechanism of action of

MUS inserted for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not mobility of the bladder neck [109]. Following MUS surgery, a wider gap between symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [110]. One study of 72 women post-synthetic suburethral MUS surgery has investigated the usefulness of translabial US to assess tape functionality. In this study different parameters were measured (distance from tape to urethra, position and shape during Valsalva manoeuvre, etc.) and concluded that tape position relative to the patient's urethra seems to play a role in treatment outcome [318]. The general role of US in the evaluation and follow-up of women with SUI is unclear, and further research is needed to establish its place in the clinical pathway.

Several imaging studies have investigated the relationship between sphincter volume and function [319] and sphincter volume and outcome of surgery [320] in women. However, no imaging test has been shown to predict the outcome of treatment for SUI. Imaging of the pelvic floor can identify levator ani detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of SUI.

4.2.3.6.1 Summary of evidence and recommendation for imaging

Summary of evidence	**LE**
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with UI.	2b

Recommendation	**Strength rating**
Do not carry out imaging of the upper or lower urinary tract as part of the routine assessment of stress urinary incontinence.	Strong

*4.2.4 **Disease management***

4.2.4.1 Conservative management

4.2.4.1.1 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for LUTS and SUI in many epidemiological studies [144, 145]. There is evidence that the prevalence of both UUI and SUI increases proportionately with body mass index (BMI) [321]. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population [145].

All the available evidence relates to women. Three SRs concluded that weight loss was beneficial in improving UI [143, 144, 322]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [323-327]. Two large studies in women with diabetes mellitus, for whom weight loss was the main lifestyle intervention, showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [323, 328]. There have been other cohort studies and case–control studies suggesting similar effects, including surgery for the morbidly obese [329-333].

In a prospective study in 160 consecutive women who underwent bariatric surgery, surgically induced weight loss was associated with a significant improvement in pelvic floor disorders, including UI [334]. Similar results reported by prospective single-centre studies investigating the effect of weight loss induced by bariatric surgery revealed that bariatric surgery was associated with substantially reduced UI at eleven months and three years [335, 336].

4.2.4.1.1.1 Summary of evidence and recommendation for obesity and weight loss

Summary of evidence	**LE**
Obesity is a risk factor for LUTS and UI in women.	3
Non-surgical weight loss improves UI in overweight and obese women.	1a
Surgical weight loss improves UI in obese women.	1b

Recommendation	**Strength rating**
Encourage overweight and obese women with LUTS/stress urinary incontinence to lose weight and maintain weight loss.	Strong

4.2.4.1.2 Urinary containment

The evidence for urinary containment derives from the same literature as for containment in OAB-wet. The readers are therefore referred to Section 4.1.4.1.3.

4.2.4.1.2.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	LE
Pads are effective in containing urine.	1b

Recommendations	Strength rating
Ensure that women with stress urinary incontinence (SUI) and their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of SUI, either for temporary symptom control or where other treatments are not planned.	Strong

4.2.4.1.3 Pelvic floor muscle training

Pelvic floor muscle training is used to improve function of the pelvic floor, thus improving urethral stability. An immediate effect of a single PFM contraction is narrowing of the levator hiatus area, increase of urethral closure pressure, and lifting of the bladder and rectum thus preventing occurrence of SUI [337-339]. In an RCT comparing intensive PFMT over a six-month period with no treatment, there were increased muscle strength and endurance, narrowing of the levator hiatus, reduced PFM length, increased muscle volume, and lifting of the bladder neck and rectal ampulla [340]. Pelvic floor muscle training may be used to prevent SUI; e.g., in childbearing women before birth, or as part of a planned recovery programme after childbirth. Most often, PFMT is used to treat existing SUI; sometimes in combination with observation and/or palpation of the muscle contraction by the therapist, or biofeedback (using an apparatus measuring the contraction either by electromyography, manometry, dynamometry, US or MRI). Electrical stimulation and vaginal cones are also used in treatment of SUI based on an assumption of the same mechanism of action.

4.2.4.1.3.1 Efficacy of pelvic floor muscle training

A Cochrane review compared PFMT with no treatment or inactive control treatment and found that women with SUI in the PFMT groups were eight times more likely to report cure (56% vs. 6%; four trials including 165 women; high-quality evidence) [341]. The review also documented significant improvement in SUI (seven trials, 376 women; moderate-quality evidence), and improvement in UI QoL (six trials, 348 women; low-quality evidence). Pelvic floor muscle training reduced leakage by one episode per day in women with SUI (seven trials, 432 women; moderate-quality evidence). Women with SUI in the PFMT groups lost significantly less urine in short (up to one-hour) pad tests. The comparison of short pad tests showed considerable heterogeneity but the findings still favoured PFMT when using a random-effects model (mean difference 9.71 g in four trials including 185 women; moderate-quality evidence). Women in the PFMT group were also more satisfied with treatment and their sexual outcomes were better. Adverse events were rare and minor.

A Cochrane review concluded that there may be some additional effect of adding biofeedback to PFMT. However, this was based on RCTs with training frequency and attention favouring biofeedback [342]. In a recent RCT (61.3% had MUI) comparing the exact same training dosage and attention between groups, use of biofeedback did not yield any additional effect [343]. Group training is cost-effective in treatment of SUI/UI compared to individual treatment [344]. Another Cochrane review concluded that combination of individual assessment/education and group training was equally effective compared to individual treatment, but again the dosage and attention differed between comparison groups [345]. In a more recent RCT with the exact same training dosage and attention in individual and group training, group training was not inferior to individual treatment [344]. It is worth noting that all of the PFMT interventions in these reviews follow individual assessment and teaching before starting PFMT, and most interventions use some sort of measurement tool (biofeedback) in the assessment.

Both the Cochrane review and the International Consultation on Incontinence (ICI) concluded that the use of vaginal cones to train the PFMs is more effective than no treatment, but it is inconclusive whether it is more or less effective than structured PFMT [341, 346, 347]. Some women are unable to maintain the cone inside, and some report discomfort and motivation problems and adherence may be low [346].

The Cochrane review [341], the ICI [347] and the National Institute for Health and Care Excellence (NICE) guidelines (2019) [67] all conclude that there is the highest level evidence (1a) to support PFMT in the treatment of SUI/MUI. All SRs conclude that PFMT is less effective if women with MUI and UUI are included in the studies and more effective with more intensive and supervised training. According to the NICE guidelines literature review, PFMT is as effective as surgery for around half of women with SUI, and due to the risks following surgery and absence of adverse effects of PFMT, they recommend three months of supervised PFMT as first-line treatment for SUI and MUI [67].

Pelvic floor muscle treatment was compared to synthetic MUS surgery in an RCT involving 460 women with moderate to severe SUI [348]. Crossover between treatment arms was allowed and 49.0% of women in the physiotherapy group and 11.2% of women in the surgery group crossed over to the alternative treatment. Subjective improvement was reported by 90.8% of women in the surgery group and 64.4% of women in the physiotherapy group at twelve months.

4.2.4.1.3.2 Efficacy of electrical stimulation

There is lack of consensus regarding the use of ES to treat SUI. For subjective cure of SUI, a Cochrane review found moderate-quality evidence that ES is probably better than no active treatment, risk ratio (RR): 2.31 [349]. Similar results were found for cure or improvement of SUI (RR: 1.73), but the quality of evidence was low. There is uncertainty as to whether there is a difference between ES and sham treatment in terms of subjective cure alone because of the very low quality of evidence (RR: 2.21). For subjective cure or improvement, ES may be better than sham treatment (RR: 2.03). Any comparison between ES and PFMT and other treatments is hampered by low-quality evidence. Adverse effects such as pain and discomfort have been reported, and ES is not tolerated by all women [349].

In an RCT, 132 women assessed by vaginal palpation to have 0–1 on the modified Oxford grading scale (unable to contract the PFM) were randomly assigned to an eight-week intervention of learning to contract via palpation, palpation with pelvic tilt, intravaginal ES, or verbal instruction [350]. The results showed that 63.6%, 69.7%, 33.3% and 18.2% in the four groups, respectively, scored two after the intervention. Palpation was significantly more effective that ES, but one third of the ES group had learned a correct PFM contraction [350]. The effect on UI measured by ICIQ-UI-SF was significantly better in the palpation group.

4.2.4.1.3.3 Long-term efficacy of pelvic floor muscle training

In a SR including nineteen studies, 1141 women were followed-up for one to fifteen years after PFMT for SUI [351]. Meta-analysis was not performed due to high heterogeneity of outcome measures and training dosage (frequency, intensity, duration and adherence). Only two studies provided interventions during follow-up. Losses to follow-up ranged between 0% and 39%. Long-term adherence to PFMT varied between 10% and 70%. Five studies reported that the initial success rate on SUI and MUI was maintained in the long term. Long-term success based on responders in the original trial varied between 41% and 85%. Surgery rates in the long term varied between 4.9% and 58%. It was concluded that short-term outcome of PFMT can be maintained at long-term follow-up without incentives for continued training, but there is a high heterogeneity in both interventional and methodological quality in short- and long-term PFMT studies [351].

4.2.4.1.3.4 Efficacy of pelvic floor muscle training in childbearing women

Pelvic floor muscle training to prevent SUI has been studied during pregnancy and in the postpartum period and the results are not reported separately for SUI and other subgroups of UI. A Cochrane review concluded that PFMT in women with and without UI (combined primary and secondary prevention) during pregnancy, produced a 26% reduced risk of UI during pregnancy and the mid-postnatal period [352]. Furthermore, pregnant continent women (primary prevention) who exercised the PFM during pregnancy were 62% less likely to experience UI in late pregnancy and had 29% lower risk of UI three to six months after giving birth. There is insufficient evidence for a long-term effect of antenatal PFMT beyond six to twelve months postpartum. Compared with usual care, there is no evidence that antenatal PFMT in incontinent women decreases incontinence in late pregnancy (very low-quality evidence), or in the mid- (low-quality evidence) or late postnatal periods (very low-quality evidence).

There have been fewer RCTs in the postpartum period than during pregnancy [352]. No primary prevention studies were found in women after birth. For PFMT started after delivery, in a mixed group of continent and incontinent women, there was uncertainty about the effect on UI risk in the late postnatal period (three trials, 826 women; moderate-quality evidence), and in postnatal women with persistent UI, there is no evidence that PFMT results in a difference in UI at more than six to twelve months postpartum (three trials; 696 women; low-quality evidence). However, another RCT found that UI was less frequent in the intervention group, with 57% of

patients still symptomatic, compared to 82% of controls, as was bladder-related problems with a prevalence of 27% in the intervention vs. 60% in the control group [353]. Randomised controlled trials of high interventional and methodological quality are needed in the postpartum period.

4.2.4.1.3.5 Pelvic floor muscle training in elderly women

There have been few RCTs on conservative treatment of SUI in elderly women (> 65 years) and many of the studies combined different modalities, such as bladder training, lifestyle modifications and PFMT [354]. Some of the studies on PFMT and SUI in the general population have included women > 65 years and PFMT seems to be equally effective in elderly women. A SR on conservative management included 23 trials, with nine of moderate-to-high methodological quality, and concluded that PFMT in combination with physical training was effective in reducing UI and improving QoL [355]. Prompted voiding and toileting assistance with functional exercise reduced UI. Other behavioural interventions such as night-time prompted voiding and waking routine had no effect on UI reduction. The most recent ICI consensus publication stated that although there are limited studies of PFMT on UI in frail elderly populations, age and frailty alone should not preclude the use of PFMT in appropriate patients with sufficient cognition to participate [354]. More high-quality RCTs, both in frail and healthy older women (> 80 years of age) are needed.

A SR from the Cochrane Database found insufficient evidence to state whether or not there were additional effects by adding PFMT to other active treatments (including vaginal cones, electromagnetic stimulation, biofeedback, continence pessary, drugs) when compared with the same active treatment alone for female SUI or mixed UI. However, these results should be interpreted with caution as most of the comparisons were investigated in small, single trials. Also, none of the included trials reported data on adverse events associated with the PFMT regimen, thereby making it very difficult to evaluate the safety of PFMT [356].

4.2.4.1.3.6 Summary of evidence and recommendations for pelvic floor muscle training

Summary of evidence	**LE**
Pelvic floor muscle training is better than no treatment for improving SUI and QoL in women with SUI and MUI across a range of outcomes, including cure rate, improvement rate, QoL, number and volume of urine leaks and treatment satisfaction.	1a
Pelvic floor muscle training exhibits a low rate of adverse events.	1a
Higher-intensity, supervised treatment regimens confer greater benefit in women receiving PFMT.	1a
There is no extra benefit of combining PFMT with biofeedback.	1b
Short-term benefits of intensive PFMT can be maintained in the long term.	2a
Pelvic floor muscle training in the antenatal period is associated with a reduced risk of UI in late pregnancy and in the short-term postnatally.	1a
Postpartum PFMT is effective in women with persistent UI.	1b
There is no benefit of postpartum PFMT in mixed (continent and incontinent) groups of women.	1b
Mid-urethral sling surgery is superior to PFMT for women with moderate-to-severe SUI.	1b
Pelvic floor muscle training commencing in the early postpartum period improves UI in women for up to 6 months.	1b
There is conflicting evidence on whether the addition of ES increases the effectiveness of PFMT alone.	2a

Recommendations	**Strength rating**
Offer supervised intensive pelvic floor muscle training (PFMT), lasting at least three months, as first-line therapy to all women with stress urinary incontinence (SUI) or mixed urinary incontinence (including elderly women and pre- and postnatal women).	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Balance the efficacy and lack of adverse events from PFMT against the expected effect and complications from invasive surgery for SUI.	Strong
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for treatment of SUI.	Strong

4.2.4.1.4 Electromagnetic stimulation

Electromagnetic stimulation (EMS) has been evaluated for its role in SUI therapy. In a double-blind RCT of EMS including 70 women with SUI, no effect of EMS over sham in any outcome was recorded [357].

4.2.4.1.5 Electroacupuncture

A SR including fifteen RCTs and women with SUI treated by electroacupuncture (EA) demonstrated that EA for SUI was effective (odds ratio [OR]: 5.64; 95% CI: 4.19-7.59; I^2: 22%). ICIQ-SF scores increased (SMD: -0.48; 95% CI: -0.62 to -0.33; I^2: 32%) and 1-hour urine leakage decreased (OR: -4.14; 95% CI: -4.69 to -3.33; I^2: 78%) in patients undergoing EA compared with those receiving sham EA, physical exercise or medication [358].

4.2.4.2 Pharmacological management

4.2.4.2.1 Oestrogen

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause.

Oestrogen treatment for SUI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [256-258]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in postmenopausal women.

A Cochrane review looked at the use of oestrogen therapy in postmenopausal women given local oestrogen therapy and seventeen studies focused on SUI [256]. There is also a narrative review of oestrogen therapy in urogenital diseases [359]. The Cochrane review found that vaginal oestrogen treatment improved symptoms of SUI in the short-term [256]. There were small, low-quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, ES and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes, although more women preferred the ring device. In one trial, no significant adverse effects following vaginal administration of oestradiol for vulvovaginal atrophy over two years were reported [360].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. The ideal treatment duration and the long-term effects are uncertain. A review of local oestrogen treatment showed improvement of UI over placebo with vaginal rings, which were favoured subjectively over pessaries [361].

One RCT in postmenopausal women showed a benefit of adding intravaginal oestriol to vaginal ES and PFMT in female SUI [362].

Studies of systemic HRT with non-urogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo and no SUI improvement [363-368]. In a single RCT, use of raloxifene was not associated with development or worsening of UI [369]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [67, 370, 371].

4.2.4.2.1.1 Summary of evidence and recommendations for oestrogens

Summary of evidence	**LE**
Vaginal oestrogen therapy improves SUI for postmenopausal women in the short-term.	1a
Neoadjuvant or adjuvant use of local oestrogens is ineffective as an adjunct to surgery for SUI.	2b
Systemic HRT using conjugated equine oestrogens does not improve SUI and may worsen pre-existing UI.	1a

Recommendations	**Strength rating**
Offer vaginal oestrogen therapy to postmenopausal women with stress urinary incontinence (SUI) and symptoms of vulvo-vaginal atrophy.	Strong
In women taking oral conjugated equine oestrogen as hormone replacement therapy (HRT) who develop or experience worsening SUI, discuss alternative HRT.	Strong

4.2.4.2.2 Duloxetine

Duloxetine inhibits the presynaptic reuptake of neurotransmitters, serotonin (5-hydroxytryptamine; 5-HT) and

noradrenaline (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurons, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

Duloxetine was evaluated as a treatment for female SUI or MUI in three SRs [170, 372, 373]. Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in the Urinary Incontinence QoL questionnaire was not found in the study, which used this as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [374], duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment in this trial.

Two open-label studies with a follow-up of ≥ 1 year evaluated the long-term effect of duloxetine in controlling SUI [375, 376]. Both studies had a high patient withdrawal rate, due to lack of efficacy and a high incidence of adverse events, including nausea and vomiting (≥ 40% of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue.

A SR showed significant efficacy for duloxetine compared to placebo in women with SUI, but with increased risk of adverse events [373]. The adverse effects of duloxetine include mental health problems and suicidal ideation. A meta-analysis of four RCTs including 1910 women with SUI reported no suicidality, violence or akathisia events, but suggested that discontinuation rate due to adverse events was around one in seven and that the harm may outweigh the benefit of treatment [377]. A meta-analysis of twelve placebo-controlled trials involving almost 3000 patients showed that, in patients with major depressive disorders, there were no significant differences in the incidence of suicide-related events with duloxetine vs. placebo [378].

4.2.4.2.2.1 Summary of evidence and recommendations for duloxetine

Summary of evidence	**LE**
Duloxetine improves SUI in women, but the chances of cure are low.	1a
Duloxetine may cause significant gastrointestinal and central nervous system adverse effects, leading to a high rate of treatment discontinuation, although these symptoms may be limited to the first weeks of treatment.	1a

Recommendations	**Strength rating**
Offer duloxetine (where licensed) to selected patients with stress urinary incontinence unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Strong
Duloxetine should be initiated and withdrawn using dose titration because of the high risk of adverse events.	Strong

4.2.4.2.3 Adrenergic agonists

A SR from the Cochrane Database including 22 RCT involving 673 women and seven different adrenergic drugs (phenylpropanolamine in eleven trials, midodrine in two, norepinephrine in three, clenbuterol in another three, terbutaline in one, eskornade in one and Ro 115-1240 in one) found weak evidence that adrenergic agonists may improve SUI. Moreover, side effects did occur but were usually minor. More evidence is needed to compare adrenergic drugs with other drugs for SUI and also with PFMT [379].

4.2.4.3 Surgical management

4.2.4.3.1 General considerations

The use of polypropylene mesh as synthetic MUS for the treatment of SUI has recently come under scrutiny following concerns about long-term complications. In some European countries such as the UK, the use of synthetic MUS has been paused and pelvic mesh was the subject of a parliamentary review published in July 2020 [380]. This review concluded that *"For many women mesh surgery is troublefree and leads to improvements in their condition. However, this is not the case for all. There is no reliable information on the true number of women who have suffered complications. While they may be in the minority, that does not diminish the catastrophic nature of their suffering or the importance of providing support to them and learning from what has happened to them".*

The range of complications highlighted during the process of this parliamentary review included [380]:

- pain;
- recurrent infections;
- mobility issues;
- recurring or new incontinence/urinary frequency;
- recurring or new prolapse;
- haemorrhage;
- bowel issues;
- erosion of mesh; this can be into the vagina and/or other organs;
- sexual difficulties; including pain on intercourse and a loss of sex life;
- autoimmune issues;
- psychological impacts.

When considering the choice of surgical treatments for SUI the Panel advises individual clinicians to abide by any national or local rules that may be in place regarding mesh surgery. It is essential for clinicians to point out the deficiencies in the long-term evidence regarding mesh use in SUI with specific reference to the complications highlighted above.

In line with the recommendations from NICE [67] and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) paper [381], the Panel agrees that surgeons and centres performing surgery should:

- be trained in the field of incontinence and for each surgical procedure they perform/offer;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for long-term follow-up.

The establishment of accurate and complete databases registering the interventions, patient profiles and surgical complications or all surgical treatments for SUI is recommended to allow the generation of robust long-term data.

Many surgical procedures are available for uncomplicated SUI patients and the Panel analysed the results of the different procedures in terms of clinical effectiveness, safety and cost-effectiveness based on the recent ESTER SR and economic evaluation [382] and previous SRs including those from the Cochrane Collaboration [383-387].

The outcome parameters used to evaluate surgery for SUI have been limited to:

- continence rate;
- patient-reported outcome measures;
- general and procedure-specific complications;
- generic, specific (UI) and associated (sexual and bowel) QoL.

In this context, it has to be taken into account that a number of products may no longer be available and therefore the recommendations may not be transferable to current devices. The Panel makes a strong recommendation that new devices are only used as part of a structured research programme and their outcomes monitored in a registry, until there is adequate evidence of safety and efficacy.

4.2.4.3.1.1 Recommendations for surgical treatment

Recommendations	Strength rating
Offer patients who have explored/failed conservative treatment options a choice of different surgical procedures, where appropriate, and discuss the advantages and disadvantages of each approach.	Strong
Use new devices for the treatment of stress urinary incontinence only as part of a structured research programme. Their outcomes must be monitored in a registry or as part of a well-regulated research trial.	Strong

4.2.4.3.1.2 Shared decision making

The Panel recognises that a shared decision-making approach is paramount when any treatments are proposed but felt particular emphasis should be made for the topic area of surgical treatment for incontinence.

There are a number of different options available for patients which vary in both efficacy and safety profile. Consequently, the amount of information given to patients considering surgery for SUI is substantial. The Panel would unequivocally advise adherence to the fundamental principles of the shared decision-making process which include:

- full participation from the patient;
- delivery of factual information regarding benefits and risks of any particular treatment, if possible adapted to the specific situation of the patient;
- delivery of information about the experience and expertise of the HCP/institution delivering the treatment, especially for highly-specialised procedures such as complex SUI and mesh removal surgery;
- confirmation that the patient understands the information given;
- clinician understanding and documenting individual patient preferences;
- facilitation of deliberation and initial decision-making;
- patient opportunity to consider and confirm any decisions made;
- clinician assistance with implementation of the final decision.

4.2.4.3.2 Surgery for women with uncomplicated stress urinary incontinence

The principal procedures evaluated are:

- open and laparoscopic colposuspension;
- autologous “traditional” slings;
- bulking agents;
- synthetic MUS.

4.2.4.3.2.1 Open- and laparoscopic colposuspension surgery

Open colposuspension was previously considered the most appropriate surgical intervention for SUI, and was used as the comparator in RCTs of newer, less-invasive surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

Open colposuspension

A number of SRs have covered open surgery for SUI, with a large number of RCTs [382, 384-387]. The Cochrane review on open colposuspension [387] included 55 trials comprising 5417 women. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Within the first year, complete continence rates of 85–90% were achieved for open colposuspension, while failure rates in terms of recurrent UI were 17% up to five years and 21% at > 5 years. The risk of reoperation after Burch colposuspension is estimated at 6% within five years [78] and 10.8% within nine years [388]. The reoperation rate specifically for UI was only 2%. Colposuspension was associated with a higher rate of development of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) at five years compared to tension-free vaginal tape (TVT) (23% and 32%, respectively). The rate of cystocoele was similar after colposuspension (37%) and after TVT (41%). The Cochrane review concluded that open colposuspension is an effective treatment for SUI and around 70% of women can expect to be dry at five years after surgery.

Laparoscopic colposuspension

A Cochrane review reported on twelve trials comparing laparoscopic to open colposuspension [385]. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were poorer for laparoscopic colposuspension. The ESTER SR [382] showed, based on a network meta-analysis, that at twelve months open colposuspension was more effective than laparoscopic colposuspension (nine trials) but these findings were based on low-quality evidence. The Surface Under the Cumulative Ranking (SUCRA) score, which is a numerical representation of the overall ranking and presents a single number associated with each intervention, was 76.7% after open colposuspension and 48.9% after laparoscopic colposuspension. Laparoscopic colposuspension had a shorter duration and subsequent hospital stay and may be slightly more cost-effective when compared with open colposuspension after 24 months’ follow-up. Single-port laparoscopic Burch can be an alternative treatment, although data confirming efficacy are limited [389].

Complications

Voiding difficulties are more common after laparoscopic colposuspension than after retropubic MUS (7.5% vs. 5.1%) [382]. There was no difference between open colposuspension and retropubic MUS (7.8% vs 7.5%; OR: 0.87) [382]. The results for the comparisons of *de novo* symptoms of urgency or UUI between open colposuspension and retropubic MUS (11% vs. 8%; OR: 1.49) did not favour either treatment and showed wide confidence intervals [382]. The rate of bladder or urethral perforation was higher for laparoscopic colposuspension compared with open colposuspension (3.7% vs. 0.7%; OR: 4.65) [382].

4.2.4.3.2.1.1 Summary of evidence and recommendation for open and laparoscopic colposuspension surgery

Summary of evidence	LE
High subjective cure rates are associated with both open and laparoscopic colposuspension for treatment of SUI.	1a
Objective cure rates are higher for open compared to laparoscopic colposuspension.	1a
Colposuspension is associated with a higher long-term risk of POP than MUS.	1a
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a
Laparoscopic colposuspension is associated with higher rates of intraoperative bladder perforation and postoperative voiding dysfunction compared to open colposuspension.	1a
The rates of *de novo* urinary urgency following colposuspension are similar to other surgical treatments for SUI.	1a

Recommendation	Strength rating
Offer colposuspension (open or laparoscopic) to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.2 Autologous sling

In the past, autologous, cadaveric, xenograft, and synthetic materials have been used for bladder neck pubovaginal sling. Nowadays, use of autologous tissue, either rectus sheath or fascia lata, is the most studied material with the strongest evidence base to support its use [390]. The ESTER SR included three trials of autologous sling vs. open colposuspension, six trials of autologous sling vs. retropubic MUS and one trial of autologous sling vs. transobturator MUS. The quality of evidence was overall very low. The pooled estimate showed that fascial sling had a higher cure rate at one year than open colposuspension (OR: 1.24), retropubic MUS (OR: 1.06) and transobturator MUS (OR: 1.44) but without significance. The SUCRA score was 89.4% for women cured after autologous fascial sling. A sub-analysis from a Cochrane review showed autologous slings had better effectiveness compared to colposuspension at one to five years' follow-up [387]. In an RCT of Burch colposuspension vs. autologous slings, complete continence rates decreased substantially over time in both arms. At five years, the continence rate of colposuspension was 24.1% compared to 30.8% for fascial slings. Satisfaction remained higher in the sling group (83% vs. 73%) and was directly related to continence status [391].

Complications

Adverse events rates were similar for the two treatment groups (Burch 10% and sling 9%) although postoperative obstruction was found exclusively in the sling group. Voiding difficulties appear to be more common after autologous sling (15.4% vs. 10.2%; OR: 1.46) than after retropubic MUS. Compared with open colposuspension, the rate of bladder or urethral perforation was lower for traditional sling (0.6% vs. 3.0%; OR: 0.20) [382].

4.2.4.3.2.2.1 Summary of evidence and recommendation for autologous sling

Summary of evidence	LE
High cure rates are associated with autologous sling placement for treatment of SUI.	1a
Autologous sling is more effective in terms of cure rate than colposuspension.	1a
Autologous sling has a similar rate of adverse events compared to open colposuspension, with higher rates of voiding dysfunction and postoperative UTI, but lower rates of POP and bladder or urethral perforation.	1a

Recommendation	Strength rating
Offer autologous sling placement to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.3 Urethral bulking agents

The concept of this procedure originates from the idea that intra- or periurethral injection of an agent able to form artificial cushions under/around the urethra increases resistance at the bladder outlet and facilitates continence.

Two Cochrane reviews (2012 and updated in 2017) identified fourteen RCTs or quasi-RCTs of treatment for UI in which at least one management arm involved peri- or transurethral injection [392, 393]. Five additional reviews investigated the effect of injectables for the treatment of female SUI [394-398] independently of the injected material. One review included results from RCTs only [398]. In the most recent Cochrane review, 1814 patients were included from fourteen trials of seven different types of intraurethral injection: glutaraldehyde cross-linked collagen (Contigent©), a porcine dermal implant (Permacol©), solid silicone elastomer (Macroplastique©), autologous fat, pyrolytic carbon (Durasphere©), calcium hydroxylapatite (Coaptite©), hydrogel (Bulkamid®) and dextran polymer (Zuidex©). The conclusions state that the available evidence base remains insufficient to guide practice [393].

A SR of 23 studies using Macroplastique© including 958 patients showed a 75% improvement with 43% dry rate at < 6 months and a 64% improvement and 36% cure rate at > 18 months [395]. A review of 514 elderly women with SUI treated with various agents showed a reduced pad weight in 73% at one-year follow-up, independent of the material injected [399]. The heterogeneity of the populations, the variety of materials used and the lack of long-term follow-up limit guidance for practice. Most of the studies showed a tendency for short-term improvement in UI, with the exception of one RCT, which did not find a difference between saline and fat injection [400].

One trial of 30 women showed a weak, non-significant advantage in terms of patient satisfaction after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels [393]. Two trials found a higher risk of urinary retention with intraurethral injections compared with transurethral injections, although the latter were associated with a higher risk of temporary urinary retention [392, 401]. A small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [402]. One study treated patients who had received radiotherapy with injection of Bulkamid® and reported ~25% cure at short-term follow-up [403].

Bulking agent injection is generally safe and the most frequent adverse event is UTI. However, autologous fat or hyaluronic acid should not be used due to the risk of fatal embolism and local abscess formation, respectively [392, 400].

Comparison with other surgical procedures

Two RCTs compared collagen injection to conventional surgery for SUI (silicon particles vs. autologous sling and collagen vs. other surgical procedures). The studies reported greater efficacy but higher complication rates for open surgery [404, 405].

In a recent non-inferiority clinical trial, women with primary SUI were randomised to TVT or polyacrylamide hydrogel urethral bulking agent injection (Bulkamid®) [406]. Mid-urethral TVT slings were associated with better satisfaction and cure rates than Bulkamid® in primary SUI. For objective cure rate, the cough stress test was negative in 95.0% of patients who underwent TVT vs. 66.4% who underwent Bulkamid®.

Another SR examining the relative efficacy of urethral bulking agents [407] included six studies in the quantitative synthesis for a total of 710 patients. The authors found that bulking agents are less effective than other surgical procedures according to subjective improvement after treatment (Relative risk [RR]: 0.70; 95% CI: 0.53-0.92, p = 0.01). However, the main limitation of this SR and meta-analysis was the absence of a common objective outcome measure to evaluate effectiveness.

4.2.4.3.2.3.1 Summary of evidence and recommendations for urethral bulking agents

Summary of evidence	**LE**
Urethral bulking agents may provide short-term improvement and cure in women with SUI.	1b
Bulking agents are less effective than MUS, colposuspension or autologous sling for cure of SUI and repeat injections may be required in order to achieve sustained benefits.	1b
Autologous fat and hyaluronic acid as bulking agents have a higher risk of adverse events.	1a
Adverse event rates for urethral bulking agents are lower compared to open surgery.	2a

There is no evidence that one type of bulking agent is better than another.	1b
The periurethral route of injection of bulking agents may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations	Strength rating
Offer urethral bulking agents to women seeking surgical treatment for stress urinary incontinence (SUI) following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Offer urethral bulking agents to women with SUI who request a low-risk procedure with the understanding that efficacy is lower than other surgical procedures, repeat injections are likely, and long-term durability and safety are not established.	Strong
Do not offer autologous fat and hyaluronic acid as urethral bulking agents due to the higher risk of adverse events.	Strong

4.2.4.3.2.4 Laser treatment

A SR including sixteen published studies, involving 899 patients with SUI, evaluated effects of laser treatment. The change in the ICIQ-SF score at one, two and sixth months was -5.49 (95% CI: -6.74 to -4.24; I^2: 91%; p<0.01), -4.97 (95% CI: -6.24 to -3.71), and -5.48 (95% CI: -6.15 to -4.81), respectively. The improvement in an one-hour pad weight test results at one, three and twelve months post treatment was -5.59 (95% CI: -6.93 to -4.25), -4.96 (95% CI: -6.73 to -3.20), and -5.82 (95% CI: -6.77 to -4.87), respectively. The PISQ-12 score increased by 5.39 (95% CI: 1.20-9.58) following treatment. Subgroup analysis identified the type and severity of UI as the potential source of heterogeneity. Adverse effects were reported in sixth of the sixteenth trials and affected only a small number of patients. Most adverse events were mild or moderate and required no medical intervention or resolved in a few days. According to this SR, vaginal laser therapy appears to be a safe, effective, and minimally invasive treatment option for SUI that can be well tolerated by patients [408].

Another SR including a total of 27 studies, evaluated the effects of Er:YAG and Fractional CO_2 lasers. The overall quality of studies was poor, and 23/27 studies were case series (LE:4). Er:YAGlaser showed a modest reduction in mild SUI cases, with benefits lasting a maximum of thirteen to sixteen months. Fractional CO_2 laser showed an improvement of mild SUI in few studies; however, no long-term data are available. When reported, adverse events were insignificant, however, they were not reported systematically [282].

Overall, SR have been noted in the current literature regarding vaginal lasers, including variation in laser settings and protocols, short-term follow-up, lack of urodynamic evaluation, and poor reporting of appropriate objective measures and adverse events. Based on the available literature, lasers cannot currently be recommended as a treatment option for SUI.

4.2.4.3.2.4.1 Summary of evidence and recommendations for laser treatment

Summary of evidence	LE
Several limitations have been noted in the current literature regarding vaginal laser treatment for SUI. These include variation in laser settings and protocols, short-term follow-up, lack of urodynamic evaluation, and poor reporting of appropriate objective measures and adverse events.	1b

Recommendations	Strength rating
Do not offer vaginal laser therapy to treat stress urinary incontinence symptoms outside of a well regulated clinical research trial.	Strong

4.2.4.3.2.5 Mid-urethral slings

Early clinical studies identified that non-autologous synthetic slings should be made from monofilament, nonabsorbable material, typically polypropylene, constructed as a 1–2 cm-wide mesh with a large pore size (macroporous) and coloured to facilitate removal [409]. Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

Transobturator route versus retropubic route

A Cochrane meta-analysis of MUS procedures for SUI in women was performed in 2017, spanning January 1947 to June 2014 [410]. Moderate-quality evidence from 55 studies showed variable, but comparable,

subjective cure rates between retropubic (71–97%) and transobturator (62–98%) slings in the short term (up to one year). No difference in the objective cure rate in the short term was found. However, the ESTER SR [382], based on a network meta-analysis including 36 trials of overall moderate quality, showed that at twelve months retropubic MUS was more effective than transobturator MUS (OR: 0.74). The SUCRA scores for women cured after retropubic MUS were 89.1% vs. 64.1% after transobturator MUS. However, there was no significant difference in these cure rates between the two approaches. Similarly, based on 40 moderate-quality trials, retropubic MUS performed better than the transobturator approach in terms of symptom improvement (RR: 0.76) but the difference was again not significant.

Analysis of a randomised equivalence trial of retropubic vs. transobturator MUS for the treatment of SUI in women shows similar findings. This trial confirms equivalence of objective cure rates at twelve but not at 24 months (77.3% and 72.3% objective cure rate for retropubic and transobturator surgery). For both types of MUS, subjective and objective treatment success decreased over time and equivalence of the retropubic and the transobturator routes could not be confirmed at 24 and 60 months, with retropubic MUS demonstrating an increased benefit, despite satisfaction remaining high in both arms [411]. Five years after surgical treatment, objective success was 7.9% greater in women assigned to retropubic sling compared to transobturator sling (51.3% vs. 43.4%), not meeting prespecified criteria for equivalence. Patient satisfaction decreased over five years but remained high and similar between treatment arms (retropubic sling 79% vs. transobturator sling 85%) [412].

In terms of long-term complications, data are scant but in one study *de novo* OAB developed in 14% of patients at ten years, with no significant differences between groups (TOT vs. TVT) [413]. In a multicentre prospective study of women undergoing TOT, failure of previous anti-incontinence procedures was the only predictor of recurrence of SUI [413].

A long-term cohort study of retropubic TVT showed an 89.9% objective cure rate and a 76.1% subjective cure rate at ten years. Overall, 82.6% of patients reported high satisfaction with surgery [414]. A long-term prospective study on transobturator sling showed that, at 145 months, the objective and subjective cure rates were 78.9% and 62.6% respectively; with no significant deterioration in SUI cure rates over time [415]. Another long-term follow-up study of patients treated with TVT showed a sustained response with 95.3%, 97.6%, 97.0% and 87.2% of patients being cured or improved at five, seven, eleven and seventeen years, respectively [416]. The ESTER network meta-analysis based on cure and improvement suggested that, when comparing surgical treatments for SUI, retropubic MUS, transobturator MUS and traditional sling had the highest efficacy, but this ranking does not consider the complication profile of these techniques. The short- to medium-term adverse event data are sparse [382]. The nine procedures compared in ESTER with their associated SUCRA ratings are shown in Table 3.

Table 3: SUCRA curve values for the outcome - number of women cured (indicated by %)

Procedure*	SUCRA rating
Traditional sling operations	89.4%
Retropubic MUS operations	89.1%
Open colposuspension	76.7%
Transobturator MUS operations	64.1%
Laparoscopic colposuspension	48.9%
Single-incision sling operations	39.8%
Bladder neck needle suspension	26.9%
Anterior vaginal repair	12.5%
Pelvic floor muscle training	2.6%

**Adapted from ESTER [363].*

Several health economic analyses of MUS procedures have been published with conflicting results. In a review of 26 economic evaluations and on the basis of a cost–utility and value of information analysis over a ten-year period, the authors concluded that MUS remains among the most cost-effective approaches [383]. A primary economic evaluation of retropubic vs. transobturator tapes over a five-year time period suggested that the latter may be cost-effective and cost-saving compared to the standard TVT approach [417]. Conversely, the findings from the ESTER network meta-analysis stated that over a lifetime, retropubic MUS was, on average, the least costly and most effective surgery but the level of uncertainty in these analyses was high.

Insertion using a skin-to-vagina direction versus a vagina-to-skin direction

The Cochrane review on MUS for female SUI showed no difference in the short- and medium-term subjective cure rates in vagina-to-skin (inside-out) vs. skin-to-vagina (outside-in) approaches, based on moderate-quality evidence [418]. Voiding dysfunction seems to be more frequent in the vagina-to-skin (inside-out) TOT group but this approach is associated with a lower frequency of vaginal perforations (RR: 0.25). Due to the low quality of the evidence, it is unclear whether the lower frequency of vaginal perforations with this approach is responsible for the lower rate of vaginal tape erosions. Likewise, a meta-analysis of RCTs demonstrated no significant difference in efficacy between outside-in and inside-out approaches, but vaginal perforations were, again, less frequent in the latter group (2.6% vs. 11.8%, OR: 0.21) [419]. The five-year data of a prospective, non-RCT of the two techniques showed a high objective success rate (82.6 vs. 82.5%, respectively) with no difference between the two approaches [420]. In a secondary analysis of the E-TOT study (a study of transobturator MUS in the treatment of women with urodynamic MUI), no difference in the patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to-vagina (outside-in) groups (63.2% and 65.5%, respectively; OR: 1.11) at nine years' follow-up [421].

Complications of synthetic mid-urethral slings

The ESTER network meta-analysis noted that comparative assessment of adverse events between different procedures was not always possible due to the lack of available data [382]. Direct comparisons using head-to-head meta-analyses were mainly carried out for retropubic MUS, transobturator MUS or single-incision slings. The authors did, however, comment that "For other intervention comparisons, the number of studies was generally small and the CIs wide. However, there was some evidence to suggest that bladder perforation was more likely to occur after retropubic MUS than after transobturator MUS, open colposuspension or traditional sling". In particular, the retropubic approach for MUS was associated with a significantly higher rate of bladder perforation than transobturator MUS was (5% vs. 0.2%). Regarding voiding dysfunction, 36 studies compared transobturator MUS with retropubic MUS, favouring the former (OR: 0.51). For pain, it is worth noting that it was defined and measured in many different ways across individual trials and across Cochrane reviews. Some pain outcomes were categorised by location (e.g., suprapubic) or time (e.g., short or long term). These discrepancies made it difficult to combine data from different studies. Data were available mainly for the comparison between retropubic and transobturator MUS and other surgical procedures. However, groin pain was more frequent after transobturator MUS than retropubic MUS (6.3% vs. 1.3%; OR: 3.80). Converse findings were reported for suprapubic pain, which was higher following TVT (1.2% vs. 4.0%; OR: 0.37). Visceral injury (0.5% vs. 2.4% OR: 0.36), mean operating time, intraoperative blood loss and hospital stay were lower in the transobturator than retropubic MUS groups. The overall vaginal erosion risk was low and comparable in both groups [382].

The rate of tape/mesh exposure or extrusion between retropubic and transobturator MUS was similar (2.1% vs. 2.4%; OR: 1.10). The exact time points at which measurements occurred could not be derived from the Cochrane reviews but most studies were reported to have a short follow-up period (≤ 12 months), with only a few studies having ≥ 2 years' follow-up [382]. Repeat surgery for UI was more common in the transobturator group (RR = 8.79); however, the data are limited and of low quality.

A population-based study performed in Scotland in > 16,000 women with SUI showed a similar rate of complications between mesh and non-mesh surgery [422]. However, a recent study of > 92,000 patients followed in the UK National Health Service showed a significant (9.8%) rate of complications using a more broad definition, and following patients for a longer period [423]. The level of detail regarding the precise nature of complications in this paper was poor. These findings suggest that, as with any SUI surgery, MUS can be associated with complications and fully informed consent is mandatory.

In general, the available published evidence would suggest that MUS does not seem to be associated with significantly higher rates of morbidity and complications compared to other surgeries for SUI, such as open retropubic colposuspension. Pelvic organ prolapse is more common after colposuspension while voiding dysfunction occurs more often after MUS [387]. The ESTER review has commented that the level of detail regarding short-to-medium adverse event data is poor for all SUI surgeries [382] and the Panel is aware of the recent findings from the Independent Medicines and Medical Devices Safety Review in the UK that has raised the possibility that the level of complications from synthetic MUS may be higher than the medical literature would suggest [380].

The ESTER SR included seven studies comparing reintervention after transobturator and retropubic MUS [382]. Pooled analysis of these studies showed wide CIs and considerable uncertainty around the estimated OR (twelve-month post-surgery: 1.37). At one to five years after the procedure, rates of repeat continence

surgery were higher in women undergoing transobturator MUS (18.3%) compared with retropubic MUS (0.5%), although only two studies were available for the analysis. A similar trend was observed in studies with a longer follow-up period (> 5 years) but the pooled analysis of these studies showed wide CIs. For retropubic MUS surgery, the bottom-to-top route was 10% more efficacious than top-to-bottom in terms of subjective cure and it was associated with less voiding dysfunction, bladder perforations and vaginal erosion [382].

Single-incision mid-urethral slings
Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operation. It should also be noted that some devices have been withdrawn from the market (e.g., TVT Secur®, Minitape, MiniArc®), and yet evidence relating to these devices may still be included in current meta-analyses. There is evidence to suggest that single-incision slings are quicker to perform and cause less postoperative thigh pain, but there is no difference in the rate of chronic pain. There is insufficient evidence for direct comparisons between single-incision slings, and no conclusions have been reached about differences between devices.

The ESTER SR showed, based on low-quality evidence, that at twelve months, retropubic and transobturator MUS were more effective than single-incision sling (TVT, OR: 0.50; TOT, OR: 0.68). The SUCRA score was 39.8% for women cured after single-incision slings. However, since not all single-incision devices have been assessed in a comparative RCT, it may be unsafe to assume that they are collectively technically similar or exhibit the same levels of efficacy.

Little data exists regarding the systematic reports of sling complications. When existing, the main limitations are heterogeneity of cohorts, poor long-term follow-up, and lack of evidence on the effective management of mesh-related complications [424]. A prospective registry will be required to generate meaningful outcome data and help in the complex management of patients who have mesh-related complications.

Complications of single-incision slings
Meta-analysis of comparison between single-incision sling and transobturator MUS showed similar rates of mesh erosion or extrusion between interventions (4.8% vs. 3.7%; OR: 1.23). Rates of postoperative pain were higher after retropubic MUS than after single-incision slings (19.2% vs. 6.8%; OR: 0.21).

The rate of unspecified pain was higher after transobturator MUS than after single-incision sling at twelve months (1.0% vs. 5.2%; OR: 0.24) and 24 months (1.4% vs. 10.4%; OR: 0.16). Single-incision sling was associated with more repeat surgery compared with transobturator MUS (5.1% vs. 2.9%; OR: 1.57). At > 3 years after the procedure, the repeat surgery rate was 10.3% for single-incision slings vs. 7.6% for transobturator MUS (OR: 1.42) [382].

Sexual function after synthetic mid-urethral sling surgery
A SR examining the effect of synthetic MUS on female sexual function suggested different and contradictory results between studies. More studies have shown an improvement, or no change, in sexual function because of a reduction in coital incontinence, anxiety and avoidance of sex. Dyspareunia was the most common cause of worsening of sexual function and the precise incidence is difficult to estimate as many studies did not report it [425]. A meta-analysis of outcome measures in trials of sling procedures suggests that single-incision slings are associated with a significantly higher improvement in sexual function compared to standard MUS procedures [426].

4.2.4.3.2.5.1 Summary of evidence and recommendations for mid-urethral slings

Summary of evidence	**LE**
The retropubic MUS appears to provide better patient-reported subjective and objective cure of SUI, compared with colposuspension.	1a
Synthetic MUSs inserted by the transobturator or retropubic route provide equivalent patient-reported outcomes at 1 year.	1a
Synthetic MUSs inserted by the retropubic route have higher patient-reported cure rates in the longer term.	1b
Long-term analyses of MUS cohorts showed a sustained response beyond 10 years.	2b
The retropubic route of insertion, compared with the transobturator route, is associated with a higher intraoperative risk of bladder perforation and a higher rate of voiding dysfunction.	1a
The transobturator route of insertion is associated with a higher risk of groin pain than the retropubic route.	1a

Long-term analysis of MUS showed no difference in terms of efficacy for the skin-to-vagina (outside-in) compared to vagina-to-skin (inside-out) directions up to 9 years.	2a
The top-to-bottom (inside-out) direction in the retropubic approach is associated with a higher risk of postoperative voiding dysfunction.	1b
The comparative efficacy of single-incision slings against conventional MUS is uncertain.	1a
Operating times for insertion of single-incision MUSs are shorter than for standard retropubic slings.	1b
Blood loss and immediate postoperative pain are lower for insertion of single-incision slings compared with conventional MUS.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional MUS.	1b
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, there is conflicting evidence regarding sexual function following SUI surgery.	2a
Improvement in sexual function appears higher with single-incision slings than with standard MUS.	1a

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure device, and although this device is no longer available, it is, however, still included in many systematic reviews and meta-analyses.

Recommendations	**Strength rating**
Offer a mid-urethral sling (MUS) to women seeking surgical treatment for SUI following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Inform women that long-term outcomes from MUS inserted by the retropubic route are superior to those inserted via the transobturator route.	Strong
Inform women of the complications associated with MUS procedures and discuss all alternative treatments in the light of recent publicity surrounding surgical mesh.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong

4.2.4.3.2.6 Other treatments for uncomplicated stress urinary incontinence

Intravesical balloon treatment has been explored for women with SUI. The Vesair® gas-filled intravesical balloon differs from other treatment methods in that it is not intended to increase outlet resistance or minimise urethral hypermobility but to attenuate the fluctuation of intravesical pressure when the abdominal pressure increases [427, 428]. Two sham-controlled RCTs have evaluated the Vesair® intravesical balloon [427, 429]. Both reported significant reductions in incontinence symptoms and pad weight but QoL was not significantly different between study arms. High levels of adverse events were reported in both trials as well as significant numbers of withdrawals/device removals. The most common adverse events were dysuria, urgency, gross haematuria and UTIs.

Mechanical devices have been used to treat SUI for centuries. There are several devices available which act either by supporting the bladder neck or urethra to address urethral hypermobility, or by occluding the urethral lumen. A 2014 Cochrane review of eight RCTs that included three small trials comparing mechanical devices to no treatment found inconclusive evidence of benefit [430]. Another 2014 review of mechanical devices concluded that there was insufficient evidence to support their use in women [431]. The place of mechanical devices in the management of SUI remains in question. Currently, there is little evidence from controlled trials on which to judge whether their use is better than no treatment, and large well-conducted trials are required for clarification. There is also insufficient evidence in favour of one particular device and few comparisons of mechanical devices with other forms of treatment [430].

Systematic reviews support the use of compression devices such as the adjustable compression therapy and artificial urinary sphincter (AUS) devices [432, 433]. Although these procedures are largely reserved for those with recurrent or complicated SUI (see Section 4.2.4.3.3.3 External compression devices), these recent additions to the literature include the use of some compression devices for uncomplicated SUI.

4.2.4.3.2.6.1 Summary of evidence and recommendations for other treatments for uncomplicated stress urinary incontinence

Summary of evidence	**LE**
Vesair® intravesical pressure-attenuating balloon improves SUI compared to sham control at 3 months.	1b

Vesair® intravesical pressure-attenuating balloon is associated with significant levels of adverse events.	1b
Implantation of an artificial sphincter can improve or cure incontinence in women with uncomplicated SUI.	3
Implantation of the adjustable compression therapy (ACT®) device may improve uncomplicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the ACT©.	3

Recommendations	Strength rating
Offer Vesair® intravesical balloon to women with mild-to-moderate stress urinary incontinence (SUI) who fail conservative treatment only as part of a well-conducted research trial.	Weak
Offer mechanical devices to women with mild-to-moderate SUI who fail conservative treatment only as part of a well-conducted research trial.	Strong
Inform women receiving artificial urinary sphincter or adjustable compression device (ACT®) that, although cure is possible, even in expert centres there is a high risk of complications, mechanical failure or a need for explantation.	Strong

4.2.4.3.3 Surgery for women with complicated stress urinary incontinence

This section addresses surgical treatment for women with complicated SUI as defined in Section 4.2.2.

Women with associated genitourinary prolapse are included in Section 4.7.

The principal procedures included are:

- Colposuspension or MUS (synthetic or autologous) following failed primary SUI surgery;
- External compression devices: adjustable compression therapy (ACT®) and AUS;
- Adjustable slings.

4.2.4.3.3.1 Colposuspension or mid-urethral sling (synthetic or autologous) following failed primary stress urinary incontinence surgery

Urinary incontinence following SUI surgery may indicate persistent or recurrent SUI, or the development of *de novo* UUI, or both. Careful evaluation including urodynamics is an essential part of the work-up of these patients.

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients are usually too small to allow meaningful comparisons. This means that no firm recommendations can be made regarding which modality is best for the treatment of recurrent SUI, and previous SRs have commented that in view of the absence of any evidence, clinicians must rely largely on expert opinion or personal experience when advising patients about treatment options [434].

The ESTER network meta-analysis revealed that women with transobturator MUS were more likely to undergo repeat surgery than those who had retropubic MUS, and fewer repeat operations were observed after retropubic MUS compared with other interventions [382]. A recent update of two Urinary Incontinence Treatment Network trials [435] compared the retreatment-free survival rates by initial surgical procedure. Five-year retreatment-free survival rates were 87%, 96%, 97%, and 99% for Burch colposuspension, autologous fascial sling, transobturator, and retropubic MUS, respectively. Types of surgical retreatment included autologous fascial sling (19), bulking agent (18), and synthetic sling (1). This suggests that MUS may not be preferred in cases of recurrent SUI [435]. In these cohorts, 6% of women after standard anti-incontinence procedures were retreated within five years; mostly with injection therapy or autologous fascial sling. Not all women with recurrent SUI chose surgical retreatment.

A 2019 Cochrane review attempted to summarise the data regarding different types of MUS procedures for recurrent SUI after failure of primary surgical therapy [436]. The literature search identified 58 records but all were excluded from quantitative analysis because they did not meet eligibility criteria. Overall, there were no data to recommend or refute any of the different management strategies for recurrent or persistent SUI after failed MUS surgery. Another SR looking at the effectiveness of MUS in recurrent SUI included twelve studies and reported an overall subjective cure rate following MUS for recurrent SUI after any previous surgery of 78.5% at an average 29 months' follow-up [437]. The subjective cure rate following MUS after previous failed MUS was 73.3% at follow-up of sixteen months. The authors commented that there was a lower cure rate with

transobturator compared to the retropubic tape for recurrent SUI after previous surgery. Conflicitng evidence comes from a SR assessed the effectiveness and complications of various surgical procedures for female recurrent SUI and reported on data from 350 women in ten RCTs with a mean follow-up of 18.1 months [438]. The authors found no difference in patient-reported and objective cure/improvement rates between retropubic and transobturator MUS in the setting of recurrent SUI. There was also no significant difference between Burch colposuspension and retropubic MUS in terms of patient-reported improvement or objective cure/improvement.

A SR of older trials of open surgery for SUI suggested that the longer-term outcomes of repeat open Burch colposuspension may be poor compared to autologous fascial slings [439]. Similarly, one large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for autologous fascial sling [440].

4.2.4.3.3.1.1 Summary of evidence for surgery in those with recurrent stress urinary incontinence following failed primary surgery

Summary of evidence	**LE**
Failure rates of single-incision slings appear higher than with other types of MUS.	1a
The incidence of repeat surgery is higher in those women who underwent primary transobturator compared to retropubic MUS.	1a
The five-year failure rate of Burch colposuspension appears higher than for synthetic or traditional sling procedures.	2b
Some studies suggest that retropubic synthetic MUS procedures appear to be more effective than transobturator MUS for the treatment of recurrent SUI, but this is not a consistent finding in the literature.	1a
Most procedures are less effective when used as second-line procedures.	2a
Burch colposuspension has similar short-term patient-reported or objective cure rates when compared to TVT for treatment of recurrent SUI.	1b
Autologous sling appears superior to Burch colposuspension for treatment of recurrent SUI.	2b

4.2.4.3.3.2 Adjustable slings

Although adjustable slings are most commonly used for treatment of complicated SUI, they may also be considered for uncomplicated SUI. There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definitions. Few studies have included sufficient numbers of patients or have long enough follow-up to provide useful evidence.

One adjustable sling is the Remeex system (Neomedic International®, Terrassa, Spain), which was investigated in a prospective study of 230 women with SUI [441]. After a mean follow-up of 89 months, 165 patients were cured of SUI (71.7% in the intention-to-treat [ITT] analysis, 80.5% in per protocol [PP] analysis). Forty patients remained incontinent (17.4% in ITT, 19.5% in PP). Eighty-eight patients required readjustment of the sling during follow-up.

The tension was increased in 82 cases due to recurrence of SUI and reduced in six due to outlet obstruction. The currently available adjustable sling devices have differing designs, making it difficult to draw general conclusions about them as a class of procedure.

4.2.4.3.3.2.1 Summary of evidence for adjustable slings

Summary of evidence	**LE**
There is only low level evidence to suggest that adjustable MUS devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard MUS.	4

4.2.4.3.3.3 External compression devices

External compression devices are usually used for treatment of recurrent SUI after failure of previous surgery but can be considered for primary treatment. Studies have largely included patients with profound intrinsic failure of the sphincter mechanism, characterised by low VLPP or urethral closure pressure [432, 433]. The two

intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT®) device and AUS.

ACT®: Using US or fluoroscopic guidance, the ACT® device is inserted by placement of two inflatable spherical balloons; one on either side of the bladder neck. The volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. A SR including eight studies published between 2007 and 2013 with follow-up of one to six years revealed 15–44% of patients considered that their SUI had been cured and 66–78.4% were satisfied [432]. The explantation rate was 19–31%. In these studies, a significant reduction in the number of pads used daily was consistently observed after ACT® balloon placement and QoL was significantly improved. The authors concluded that ACT® balloons constitute a reasonable, minimally-invasive alternative for treatment of female SUI due to intrinsic sphincter deficiency, especially in patients who have already experienced failure of standard surgical treatment.

AUS: The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [430]. There have been a few case series of AUS in women, with populations of 45–215 patients and follow-up of one month to 25 years [442-445]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cure in 59–88%. Common adverse effects included mechanical failure requiring revision (≤ 42% at ten years) and explantation (5.9–15%). In a retrospective series of 215 women followed-up for a mean six years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [445].

Early reports of laparoscopically implanted AUS do not have sufficient patient populations or sufficient follow-up to be able to draw any conclusions [446, 447].

A more recent SR included seventeen studies but all were retrospective or prospective non-comparative case series [433]. Most patients had undergone at least one anti-incontinence surgical procedure prior to AUS implantation (69.1–100%). Outcomes revealed that complete continence rates were 61–100%. The rates of explantation were 0–45%, erosion rates were 0–22% and mechanical failure rates were 0–44%. The authors concluded that AUS can provide excellent functional outcomes in women with SUI resulting from intrinsic urethral sphincter deficiency but at the cost of high morbidity.

4.2.4.3.3.3.1 Summary of evidence for external compression devices

Summary of evidence	**LE**
Implantation of an artificial sphincter improves or cures incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the AUS device may improve complicated SUI.	3
Implantation of the ACT® device may improve complicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and ACT®.	3
Explantation of AUS is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

4.2.4.3.3.4 Recommendations for complicated stress urinary incontinence

Recommendations	**Strength rating**
Management of complicated stress urinary incontinence (SUI) should only be offered in centres with appropriate experience (see Section: 4.2.4.3.1).	Strong
Base the choice of surgery for recurrent SUI on careful evaluation, including individual patient factors and considering further investigations such as cystoscopy, multichannel urodynamics, as appropriate.	Strong
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as second-line treatment, is generally inferior to its use as first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Only offer adjustable mid-urethral sling as primary surgical treatment for SUI as part of a structured research programme.	Strong

Consider secondary synthetic sling, bulking agents, colposuspension, autologous sling or artificial urinary sphincter (AUS) as options for women with complicated SUI.	Weak
Inform women receiving AUS or ACT® device that, although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Strong

4.2.4.3.4 Surgery for stress urinary incontinence in special patient groups

4.2.4.3.4.1 Stress urinary incontinence surgery in obese women

There is no agreement about the outcome of incontinence surgery in obese women. Secondary analysis of an RCT on retropubic and transobturator tapes for treatment of women with SUI suggests that obese women experience inferior outcome compared to non-obese women. Stratification of patients according to BMI (< 30 and ≥ 30) shows a significant difference in objective dry rates (negative pad test) at one year (85.6% vs. 67.8%) and five years (87.4% vs. 65.9%) and subjective cure (absence of SUI symptoms) at one year (85.8% vs. 70.7%) and five years (76.7% vs. 53.6%). At one and five years, 6.7% and 16.3% of patients who were initially dry (negative pad test) after surgery developed a positive pad test [448, 449].

Conversely, short-term outcome of single-incision MiniArc® sling showed comparable objective cure rates (negative cough stress test) at two years (86% and 81% in non-obese and obese women, respectively); similar improvement of the Urinary Distress Inventory 6 and Incontinence Impact Questionnaire seven was observed in non-obese and obese women [450].

4.2.4.3.4.2 Stress urinary incontinence surgery in elderly women

Age appears to be a significant factor in outcome from SUI surgery but there is conflicting evidence. An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 years [451]. An RCT assessing risk factors for the failure of TVT vs. transobturator tension-free vaginal tape (TVT-O) in 162 women also found that age was a specific risk factor for recurrence at one year [452]. In addition, based on a sub-analysis of a trial cohort of 655 women at two years' follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up, were less likely to report objective or subjective improvement in stress and UUI, and were more likely to undergo retreatment for SUI. There was no difference in time to postoperative normal voiding [453].

Another RCT comparing immediate TVT vs. no surgery (or delayed TVT) in older women, confirmed efficacy of surgery in terms of QoL and satisfaction, but with more complications in the surgical arm [454]. Conversely, a cohort study of 181 women undergoing TVT-O found that women aged > 70 years had similar outcomes when compared to women < 70 years in terms of cure rates (92.5% vs. 88.3%), voiding dysfunction, vaginal erosion and groin pain at a median follow-up of two years [455].

Furthermore, a SR of the efficacy of treatments of UI in older patients suggests that MUS is successful in older patients (≥ 65 years) with 5.2–17.6% reporting persistent SUI after surgery. No difference in the frequency of *de novo* UUI, persistent UUI or persistent SUI was found in older patients [384].

A cohort study of 256 women undergoing vagina-to-skin (inside-out) TOT reported similar efficacy in older vs. younger women, but there was a higher risk of *de novo* urgency in older patients [456].

4.2.4.3.4.3 Summary of evidence and recommendations for stress urinary incontinence surgery in special patient groups

Summary of evidence	**LE**
Incontinence surgery may be safely performed in obese women, however, outcomes may be inferior.	1
The risk of failure from surgical repair of SUI, and the risk of suffering adverse events, appears to increase with age.	2b
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendations	**Strength rating**
Inform obese women with stress urinary incontinence (SUI) about the increased risks associated with surgery, together with the lower probability of benefit.	Weak
Inform older women with SUI about the increased risks associated with surgery, together with the likelihood of lower probability of benefit.	Weak

*4.2.5 **Follow-up***

The follow-up of patients with SUI is dependent on the treatment given. For conservative and physical therapies, sufficient time should be allowed for the demonstration of a therapeutic effect. For pharmacological treatment, early follow-up is recommended. For most surgical interventions, short-term follow-up should be arranged to assess efficacy and identify any early postoperative complications.

The Panel is supportive of long-term outcome assessment via registries and recognises the paucity of high-quality long-term data, specifically regarding complications from surgery.

4.3 Mixed urinary incontinence

The term MUI is broad because it may refer to equal stress and urgency symptoms, stress-predominant symptoms, urgency-predominant symptoms, urodynamic stress urinary incontinence (USUI or USI) with DO or USUI with clinical urgency symptoms, but no DO [457]. The challenge of this broad definition is that it leads to inconsistencies when evaluating treatment options and outcomes.

*4.3.1 **Epidemiology, aetiology and pathophysiology***

The prevalence rates of MUI vary widely in the literature. Most epidemiological studies have either not considered subtypes of UI, or only reported on SUI, UUI and MUI. The current literature is unclear regarding the population prevalence and risks for the different UI subtypes [458]. There are many urinary symptom questionnaires used in epidemiological research, with varying evidence of validity. Caution is needed when comparing epidemiological studies that do or do not report a separate MUI subgroup, and when generalising from population level data to clinical practice. The problems arise from significant heterogeneity in terms of types of questionnaires/surveys used, population parameters, variable response rates, varying definitions of MUI, and outcome measures.

It seems apparent, however, that MUI is the second most common form of UI, after SUI, with most studies reporting a 7.5–25% prevalence [458]. One can extrapolate that among women with UI, approximately one-third have MUI [459]. In a secondary analysis of a large clinical trial, 655 women were evaluated for UI and their response to treatment [460]. It was found that 50–90% of women fell into the category of MUI based on patient-reported answers to the Medical Epidemiologic and Social Aspects of Aging and Urinary Distress Inventory (UDI) questionnaires. However, when objective criteria such as urodynamic findings were used, only 8% of women were categorised as having MUI.

Mixed urinary incontinence is usually caused by a combination of the same factors that cause SUI and UUI. Several factors may be responsible for its development, including oestrogen deficiency, abnormalities in histomorphology, and microstructural changes [461]. One report postulates that an incompetent sphincter and bladder neck allow urine to enter the proximal urethra during stress, causing a urethro-detrusor reflex that triggers involuntary detrusor contraction, which then causes urgency and UUI [462]. Another study has shown that urine flow across the urethral mucosa increases the excitability of the micturition reflex [463]. Ultimately, it is unlikely that one theory or risk factor can explain the development of MUI and its symptoms; it is more probable that disturbances in several elements and the lack of bladder compensation results in the development of MUI [461].

*4.3.2 **Diagnostic evaluation***

Assessment of patients with MUI begins with a thorough history of the patient's urinary symptoms and follows the recommendations set out in the general evaluation and diagnosis of LUTS section 3. It is conventional to try and categorise MUI as either stress or urge predominant.

Mixed urinary incontinence is difficult to diagnose, as the condition comprises many phenotypes. Some women exhibit detrusor contractions provoked by physical stressors, some have unprovoked detrusor contractions, and many have no abnormal detrusor contractions, but still report urine leakage with the sensation of urgency. Some women with urgency symptoms do not manifest UUI because their urethral sphincter is strong and often able to prevent urine leakage [464].

The role of urodynamics in MUI is unclear, but establishing objective degrees of SUI and DO incontinence may help in counselling patients about the most appropriate initial treatment option.

4.3.2.1 Summary of evidence and recommendations for the diagnosis of mixed urinary incontinence

Summary of evidence	LE
There is no evidence that urodynamics affects outcomes of treatment for MUI.	3

Recommendations	Strength rating
Complete a thorough history and examination as part of the assessment of mixed urinary incontinence (MUI).	Strong
Characterise MUI as either stress-predominant or urgency-predominant where possible.	Weak
Use bladder diaries and urodynamics as part of the multimodal assessment of MUI to help inform the most appropriate management strategy.	Strong

4.3.3 ***Disease Management***

4.3.3.1 Conservative management

Women with MUI generally have more severe symptoms and respond less well to treatment than women with only SUI or UUI [465]. Clinicians are encouraged to begin treatment for MUI with conservative management directed toward the most bothersome component of the symptom spectrum and to reserve surgery as a last resort [464].

4.3.3.1.1 Pelvic floor muscle training

An RCT comparing PFMT with and without an audiotape for 71 women with UI did not find any difference between the two treatment arms [466]. Mean number of incontinent episodes per day decreased from 3.9 overall to 3.2 for participants with MUI. Six months after completing the course of exercises, approximately one third of all enrolees reported that they continued to note good or excellent improvement and desired no further treatment.

A small RCT including 34 women with SUI and MUI compared eight weeks of PFMT with no treatment and found that PFMT significantly increased PFM strength, improved QoL, and reduced the frequency of UI episodes compared to no treatment [467]. Another RCT including SUI and MUI confirmed these results [468].

A multicentre randomised controlled non-inferiority trial on 467 women with MUI was conducted in ten hospitals. Participants were randomised 1:1 to receive EA (36 sessions over twelve weeks with 24 weeks of follow-up) or PFMT–solifenacin (5 mg/day) over 36 weeks. In women with moderate-to-severe MUI, EA was not inferior to PFMT–solifenacin in decreasing the 72-h incontinence episodes (between-group difference, –1.34%) [469].

In a comparative study of the effectiveness of behavioural therapy and PFMT (combined with MUS vs. sling alone in women with MUI), 416 (86.7%) had post-baseline outcome data and were included in primary twelve-month analyses [470]. The UDI score in both groups significantly decreased (178.0 to 30.7 points in the combined group, 176.8 to 34.5 points in the sling-only group). The model-estimated between-group difference, did not meet the minimal clinically important difference threshold. Adherence to the behavioural therapy and PFMT regimes, which is a prerequisite for achieving a satisfacory outcome, was not reported in the study.

A Cochrane review comparing PFMT with no or sham treatment included 31 RCTs from fourteen countries, but there was only one study including women with MUI and one with UUI and none of them reported data on cure, improvement, or number of episodes of these subgroups [341].

Another Cochrane review comparing different approaches to delivery of PFMT (21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [345]. This concurs with the latest ICI publication [347]. No other consistent differences between techniques were found.

The effect of combining biofeedback with PFMT has already been fully addressed in Section 4.2.4.1.3, and there was no evidence of any additional benefit in a population with predominantly MUI.

4.3.3.1.2 Bladder training

Details on BT programmes are given in Section 4.2.4. The ICI 2017 [347] concluded that for women with UUI or MUI, PFMT and BT are effective first-line conservative therapies. One RCT assigned 108 women with diagnoses of SUI (n = 50), UUI (n = 16), or MUI (n = 42) to sixth weeks of BT and PFMT or BT alone [471].

Overall, and in the SUI and MUI subgroups, significantly more patients in the BT and PFMT group reported cure and improved symptoms.

4.3.3.1.3 Electrical stimulation

A Cochrane review on ES for SUI included participants with SUI or stress-predominant MUI. Twenty-five percent of the included trials were deemed to have a high risk of bias due to a variety of factors, including baseline differences between groups and industry funding. For subjective cure or improvement of SUI, low-quality evidence indicated that ES was better than no active treatment or sham treatment. Electrical stimulation for OAB and SUI is covered in Sections 4.1.4.1.5.4 and 4.2.4.1.3.2.

4.3.3.2 Summary of evidence and recommendations for conservative management in mixed urinary incontinence

Summary of evidence	**LE**
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Pelvic floor muscle training is better than no treatment for improving UI and QoL in women with MUI.	1a
Bladder training combined with PFMT may be beneficial in the treatment of MUI.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer bladder training as a first-line therapy to adults with MUI.	Strong
Offer supervised intensive pelvic floor muscle training, lasting at least three months, as a first-line therapy to all women with MUI (including elderly and postnatal women).	Strong

4.3.3.3 Pharmacological management

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

4.3.3.3.1 Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI but not SUI, suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [472]. In another study (n = 1380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [473]. Similar results were found for solifenacin [474, 475].

4.3.3.3.2 Duloxetine

In one RCT of duloxetine vs. placebo, 588 women were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups, although results in the stress-predominant groups were better [476]. Treatment-emergent adverse event rate in the duloxetine group was 61.3% with discontinuation rates of 15.7%. Adverse event rates were higher in those participants taking other concomitant antidepressant agents.

Duloxetine was found to have equal efficacy for SUI and MUI in an RCT (n = 553) following secondary analysis of respective subpopulations but no adverse events data were reported [477].

4.3.3.3.3 Summary of evidence and recommendations for pharmacological management of mixed urinary incontinence

Summary of evidence	**LE**
Limited evidence suggests that anticholinergic drugs are effective for improvement of the UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and MUI symptoms, but adverse event rates are high.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI.	Strong

Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Weak

4.3.3.4 Surgical management

The surgical treatment options for MUI, include all the anti-incontinence procedures are outlined in the SUI Section 4.2.4.3.

Many RCTs include patients with pure SUI or pure UUI as well as patients with MUI. However, few RCTs report separate outcomes for MUI subgroups.

Post hoc analysis of a large RCT showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of preoperative urgency [453]. A similar *post hoc* review of another RCT comparing transobturator and retropubic MUS showed that the greater the severity of preoperative urgency, the more likely that treatment would fail [97]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO). Another RCT including 93 patients with MUI showed a significant improvement in continence and QoL in the group that had TVT and botulinum toxin A (Botox®) rather than with either treatment alone [478].

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing MUS insertion, overall satisfaction rates were lower for women with mixed symptoms and DO on preoperative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [479]. A comparison of two parallel cohorts of patients undergoing Burch colposuspension for SUI, with and without DO, found inferior outcomes in women with MUI [480].

One cohort of 450 women, showed that in urgency-predominant MUI, the success rate of TVT fell to 52% compared to 80% in stress-predominant MUI [481]. In a study of 1113 women treated with transobturator TVT, SUI was cured equally in stress- or urgency-predominant MUI. However, women with stress-predominant MUI had significantly better overall outcomes than women with urgency-predominant MUI [482].

In contrast to studies examining older surgical methods, more recent studies (generally small case series) have reported that UUI symptoms improve in 30–85% of women with MUI after MUS surgery [483].

In a prospective, multicentre, comparative trial, 42 women who had TVT for MUI had greater improvement in urgency and QoL scores than 90 women who had TOT. There were no significant differences in the cure and satisfaction rates between the two groups [484].

In a single-centre prospective study, 86 consecutive women underwent TOT for MUI. At a mean follow-up of 59 months, SUI was cured objectively in 83.7% and subjectively in 87.2% of the patients. The continence rates were 74.4% for UUI and 66.3% for MUI (cure of both components). The patient-reported success rate was 87.2% (“much better” or “very much better” on the Patient Global Impression of Improvement scale). There were significant improvements in all domains except general health. The univariate analysis found no significant risk factor for persistence of SUI. Median age > 60 years and menopause were predictive for persistence of UUI. Median and mean age > 60 years were predictive of persistence of overall incontinence [485]. Overall, the outcome for women with pre-existing UUI remains uncertain.

In a secondary analysis of a study of transobturator TVTs in the treatment of women with urodynamic MUI, no difference in patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to vagina (outside-in) groups (63.2% and 65.5%, respectively) at nine years’ follow-up [421].

Analysis of the trial populations included in the meta-analysis on single-incision slings suggests that the evidence can be generalised to women who have predominantly SUI, and no other clinically severe LUT dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI.

Research trials should define accurately what is meant by MUI. There is a need for well-designed trials comparing treatments in populations with MUI, and in which the type of MUI has been accurately defined.

4.3.3.4.1 Summary of evidence and recommendations for surgery in patients with mixed urinary incontinence

Summary of evidence	LE
Women with MUI are less likely to be cured of their UI by SUI surgery than women with SUI alone.	2
The response of pre-existing urgency symptoms to SUI surgery is unpredictable.	1b

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Warn women that surgery for MUI is less likely to be successful than surgery for stress urinary incontinence alone.	Strong
Inform women with MUI that one single treatment may not cure urinary incontinence; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	Weak

4.4 Underactive bladder

Underactive bladder is a common clinical entity, defined by the ICS as *"a symptom complex characterised by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms"* [486]. Diagnosis of UAB is based on clinical symptoms and the presentation and aetiology can be variable.

This differs from DU, which is a diagnosis based on urodynamic studies. Detrusor underactivity is defined by the ICS as *"a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"* [1]. Acontractile detrusor is specified when there is no detrusor contraction.

Female voiding dysfunction is defined by the ICS as a diagnosis based on symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or abnormally high PVR volume; ideally on repeated measurement to confirm abnormality. Pressure–flow studies may be required to determine the cause of the voiding dysfunction [31].

*4.4.1 **Epidemiology, aetiology, pathophysiology***

4.4.1.1 Epidemiology

Underactive bladder as an entity remains difficult to study, partly because its corresponding urodynamic correlate, DU, remains loosely defined, leading to significant variability in diagnostic criteria across research studies and significant overlap of symptoms with other conditions. As a consequence of the variable definition, reported prevalence also varies and ranges from 12% to 45% in women, with increased prevalence seen with age [76] and in institutionalised elderly women [487].

Several studies have demonstrated similar prevalence rates for DU in the ambulatory setting of around 12–19.4% [488-490]. As would be expected, voiding symptoms consistent with UAB are higher. A Detroit population study surveyed 291 women, with 20% reporting difficulty with bladder emptying [491]. In a large cross-sectional, population-based internet survey conducted in the USA, UK and Sweden including 15,861 women aged ≥ 40 years, 20.1% referred to weak flow, 27.4% to incomplete bladder emptying and 38.3% to terminal dribbling [5].

Some studies have identified the coexistence of DO during filling and DU in the voiding phase of urodynamic studies (formerly known as detrusor hyperactivity with impaired contractility; DHIC) as a common finding in elderly women. Up to 38.1% of incontinent institutionalised women showed DHIC in urodynamic studies [492, 493].

4.4.1.2 Aetiology

The presence of DU in diverse clinical groups suggests multifactorial aetiology [494]. Idiopathic DU is probably partly an age-dependent decrease in detrusor contractility with no other identifiable causes, but young women can also have DU. There are many secondary causes of DU, including neurogenic (e.g., multiple sclerosis, multiple systemic atrophy, spinal cord injury, spina bifida, Parkinson's disease, hydrocephalus, transverse myelitis, stroke, Guillain–Barré syndrome, diabetes mellitus, and pelvic nerve injury), myogenic (acute prolonged bladder overdistension, diabetes mellitus, and BOO) and iatrogenic (pelvic surgery) causes [495].

4.4.1.3 *Pathophysiology*

There are many pathways involved in normal detrusor contraction, and there are different possible sites of dysfunction [76] with a variety of mechanisms involved in UAB:

- Central circuits and centres (prefrontal cortex, periaqueductal gray, pontine micturition centre and hypothalamus): failure of integration or processing;
- Efferent pathways (sacral cord, sacral nerves, pelvic nerves and postganglionic neurons): impaired detrusor activation;
- Afferent pathways (peripheral afferent nerves, anterolateral white column and posterior column): early termination of voiding reflex;
- Muscle (detrusor myocytes and extracellular matrix): loss of intrinsic contractility.

Different aetiologies can share common pathophysiological mechanisms: for example, diabetes mellitus affects mainly afferent pathways and the detrusor muscle; and neurogenic diseases affect central circuits and efferent/ afferent pathways.

One study suggests that in patients with DU, there is significant urothelial dysfunction, increased sub-urothelial inflammation and apoptosis, and altered sensory protein expression [496]. Impaired urothelial signalling and sensory transduction pathways may reflect part of the pathophysiology of DU. Pelvic ischaemia is another proposed mechanism of DU in ageing patients [496] (Figure 1).

Figure 1: Management and treatment of women presenting with urinary incontinence, site of dysfunction, major aetiological factors, mechanisms

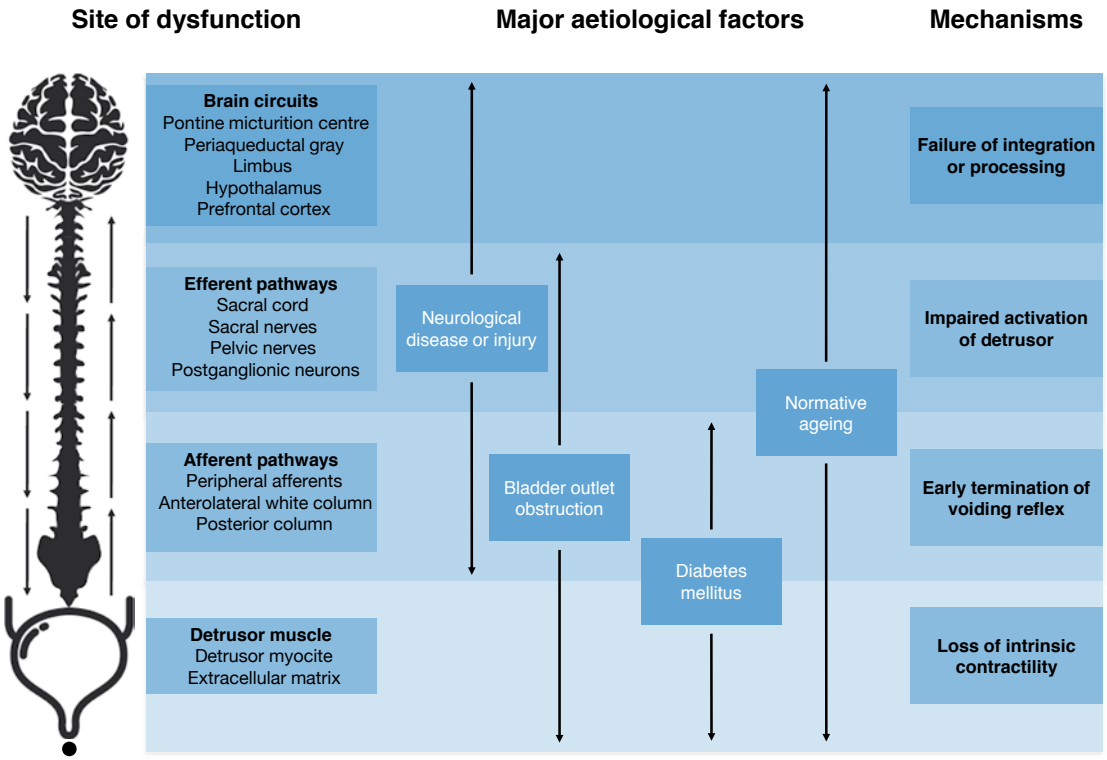


**Figure reproduced with permission from the publisher, from Osman N. et al., [473].*

4.4.2 ***Classification***

There is no current classification system of UAB. Patients can be classified according to presumed aetiology or pathogenic mechanism, but without sufficient longitudinal data or high-level evidence to establish prognostic factors, the classification of UAB patients in terms of relevant clinical characteristics or risk of complications is not possible.

4.4.3 ***Diagnostic evaluation***

4.4.3.1 *Symptoms associated with detrusor underactivity*

A retrospective study correlated LUTS with urodynamic findings in 1788 patients (1281 women). Women with DU, defined as detrusor pressure at maximum flow rate ($P_{det}Q_{max}$) < 20 cmH_2O, maximum flow rate (Q_{max}) < 15 mL/s, BVE < 90% and excluding obstruction on video-urodynamic studies, had a significantly higher

occurrence of reduced and/or interrupted stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, and absent and/or decreased sensation compared with women with normal pressure and flow [497]. A qualitative study on a small sample of male and female patients diagnosed with DU reported a variety of LUTS and associated impact on QoL. Storage symptoms of nocturia, increased daytime frequency, and urgency, and the voiding symptoms of slow stream, hesitancy, and straining were reported by over half of the patients. A sensation of incomplete emptying and post-micturition dribble were also frequently described. The impact of their symptoms on QoL was variable, but in general, storage symptoms were more bothersome [498].

Based on current data, it is not possible to find a pivotal symptom or collection of symptoms to identify DU patients. The ICI Questionnaire Underactive Bladder (ICIQ UAB) has been developed as a research PROM tool, that needs validation before use in common clinical practice [499].

4.4.3.2 Urodynamic studies

Non-invasive studies like uroflowmetry, PVR volume measurement and BVE determination are potentially useful to identify women who might have DU. There is considerable symptomatic overlap with BOO, and uroflowmetry and PVR volume findings may also be similar. Only invasive urodynamics with pressure–flow studies can reliably distinguish DU from BOO and these urodynamic diagnoses can coexist. Diagnosis in women is particularly difficult as they can void by relaxing the pelvic floor, that is, without detectable detrusor contraction during pressure–flow study and without increased abdominal pressure [500]. The simplest methods to define and diagnose DU are based on the use of cut-off values of Q_{max} and $P_{det}Q_{max}$, possibly combined with cut-off values of PVR volume and BVE. However, there is no consensus on which cut-off values should be used [501]. It is obvious that the prevalence of DU depends on the criteria used. In a retrospective study of 1015 women, DU was found in 14.9% when using Q_{max} < 12 mL/s or PVR volume > 150 mL; in 9.6% when using $P_{det}Q_{max}$ < 30 cm H_2O and Q_{max} < 10 mL/s; and in 6.4% when using $P_{det}Q_{max}$ < 20 cm H_2O, Q_{max} < 15 mL/s and BVE < 90% [502].

More elaborate methods combine urodynamic data into an index or a physical quantity that reflects bladder contraction strength. A value below a certain threshold would thus diagnose DU. Again, there is no consensus regarding what is normal/abnormal. Table 4 provides an overview of the best-known parameters, their background, and typical values. Watt's factor (WF) estimates the power generated by the detrusor per unit area of bladder surface [503] and it varies during voiding. Usually, WF_{max} is considered. Alternatively, its value at Q_{max} can be used. Projected isovolumetric pressure (PIP) is a gross simplification of the bladder output relation and estimates the maximum detrusor pressure that can be generated by the bladder when the outlet is closed; the isovolumetric detrusor pressure. The bladder contractility index (BCI) is simply a reduction of PIP to an index [504]. The population in which PIP and BCI were developed mainly consisted of men. Projected isovolumetric pressure one, is similar to PIP and also estimates the isovolumetric detrusor pressure, but was developed in an entirely female population via an experimental method [505].

A third method of quantifying bladder contraction strength involves stop tests. One study compared three types of direct measurement of isovolumetric pressure: (1) the voluntary stop test, in which the patient voluntarily interrupted flow; (2) the mechanical stop test, in which flow was interrupted by a balloon catheter; and (3) the continuous occlusion test, in which the subject tried to void against a blocked outlet. The latter had the best reliability and best detected drug-induced changes, though the results of the mechanical stop tests were similar [506].

All parameters discussed above give some information about the strength of detrusor contraction in a given void. They do not necessarily reflect what the detrusor might potentially achieve under optimum conditions [507]. Also, they give no information on the important aspect of voiding duration. No parameters for this are available. Finally, abnormally low bladder contraction strength does not necessarily imply insufficient bladder contraction strength to achieve optimal voiding. Table 4 summarises different parameters to measure detrusor contraction in female patients.

Table 4: Most used parameters to measure detrusor contraction in female patients

Parameter	Basis	Population	Values
Watt's factor (WF) [503]	Hill equation of muscle contraction in a spherical organ, with fixed constants obtained from experimental and clinical studies	Eight asymptomatic female volunteers aged 28–45 years (median 34 years)	Ideal voiding (bell-shaped flow curves): WF_{max} 11-24 W/m^2 Non-ideal voiding: WF_{max} 5–10 W/m^2 Normally WF_{max} > 7 W/m^2 (expert opinion, unspecified population) [508]
Projected isovolumetric detrusor pressure (PIP, cm H_2O) and Bladder Contractility Index (BCI), using PIP as an index [504, 509]	Bladder Output Relation, simplified to a straight line with fixed slope of 5 cm H_2O/mL/s (Formula: $P_{det}Q_{max}$ + 5xQ_{max})	Unspecified population, mainly men with BPO	Classification based on expert opinion: > 150: strong contraction 100-150: normal contraction 50-100: weak contraction < 50: very weak contraction
Projected isovolumetric detrusor pressure 1 (cm H_2O) [505]	Comparison of Q_{max} and $P_{det}Q_{max}$ values with stop test results (Formula: $p_{det}Q_{max}$ + Q_{max})	100 women with UUI aged 53–89 (mean: 70) years	5th-95th percentile: 29–78 cm H_2O Mean: 49 cm H_2O Median: 48 cm H_2O Proposed typical values: 30-75 cm H_2O
Continuous occlusion test [506]	Direct measurement of isovolumetric voiding contraction	70 women with UUI aged 53–89 (mean: 70) years	Mean ± SD: 48.7 ± 24.4 cm H_2O

BPO = benign prostatic obstruction; BCI = Bladder contractility index; PIP = Projected isovolumetric pressure; UUI = urgency urinary incontinence; WF = Watt's factor.

*4.4.4 **Disease management***

As there are so many different possible causes and pathogenic mechanisms involved in female UAB, preventive and therapeutic strategies are difficult to define. Among preventive strategies, early recognition after major surgery or labour might prevent long-term problems associated with prolonged bladder over-distension. Nerve-sparing techniques for radical pelvic surgery are more favourable in terms of early recovery of bladder function [510, 511].

Treatment of female DU includes strategies to ensure bladder drainage, increase bladder contraction, decrease urethral resistance, or a combination [508]. The management goals for UAB are to improve symptoms and QoL, to reduce the risk of complications for impaired bladder emptying, and to identify situations where interventions may not be appropriate.

4.4.4.1 Conservative management

4.4.4.1.1 Behavioural interventions

Regular or timed voiding to avoid bladder over-distension should be encouraged in women with impaired bladder sensations. Assisted voiding by abdominal straining with adequate relaxation of the PFM has been recommended, as well as double or triple voiding in an attempt to improve bladder emptying. None of these manoeuvres has proven its efficacy in a randomised study. There is a possible association between voiding by excessive abdominal straining and the risk of pelvic organ prolapse [512]. A small retrospective study in women with neurogenic acontractile detrusor secondary to spina bifida showed that Valsalva voiding may increase the risk of rectal prolapse compared with CISC [513].

4.4.4.1.2 Pelvic floor muscle relaxation training with biofeedback

There are no RCTs on PFM relaxation training in adult women with UAB. Contradictory to common beliefs, one study found significant relaxation of the PFMs after contraction [514] and another study found that PFM relaxation training over time increased the speed of relaxation after a single contraction [515]. However, muscle contraction is known to be followed by relaxation. There is some evidence from the paediatric literature, including one RCT that compared efficacy of PFM relaxation with biofeedback plus combined therapy (including hydration, scheduled voiding, toilet training and diet) vs. combined therapy alone in children with non-neuropathic UAB and voiding dysfunction. Mean number of voiding episodes was significantly increased in the relaxation training group compared with the group with only combined treatment (6.6 ± 1.6 vs. 4.5 ± 1

times a day). Postvoid residual urine volume and voiding time decreased considerably, whereas maximum urine flow increased significantly in the relaxation group compared with the combined treatment group (17.2 ± 4.7 vs. 12.9 ± 4.6 mL/s) [516].

4.4.4.1.3 Clean intermittent self-catheterisation

See Section 4.1.4.1.3 for details on CISC.

4.4.4.1.4 Indwelling catheter

Indwelling urinary catheter may be an option for some women who have failed all other treatments and are unable to perform CISC. Complications include UTI, stone formation and urethral damage. Suprapubic catheterisation may be preferable over urethral catheterisation to minimise the risk of urethral trauma and pain [517].

4.4.4.1.5 Intravesical electrical stimulation

Intravesical electrical stimulation (IVES) can be used to improve bladder dysfunction by stimulating A-delta mechanoreceptor afferents, but requires preservation of afferent circuits and healthy detrusor muscle. One retrospective study in sixteen patients (eleven females) found that two-thirds of patients with a weak detrusor after prolonged bladder over-distension regained balanced voiding after IVES due to detrusor reinforcement [518].

4.4.4.1.6 Intraurethral insert

The intraurethral insert, or prosthesis, is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. A narrative review [519] that evaluated the InFlow™ intra-urethral valve pump and activator identified seven studies of which six were industry sponsored. The studies reported a high drop-out rate (12–50%), mainly due to tolerability issues (leakage and discomfort), but discontinuation rates were found to be reduced with careful patient education and counselling prior to commencement. Amongst participants who did tolerate the device, QoL rates improved by 60% and UTI rates were marginally lower than for the standard comparator (CISC). The studies reported equivalent efficacy for the insert in terms of reducing PVR compared to CISC. The certainty of evidence from this review remains low due to clinical heterogeneity and publication bias.

4.4.4.2 Pharmacological management

4.4.4.2.1 Parasympathomimetics

Theoretical approaches to UAB pharmacological treatment include direct stimulation of detrusor cell muscarinic receptors using agonists like carbachol or bethanechol, or inhibiting acetylcholinesterase (enzyme that inhibits the endogenous muscarinic agonist acetylcholine) using agents such as distigmine, pyridostigmine or neostigmine.

A SR on the use of parasympathomimetics in patients with UAB included ten RCTs (controls typically received placebo or no treatment). Three studies reported significant improvements relative to the control group, but six did not and one even reported significant worsening of symptoms. There was no evidence for differences between individual drugs, specific uses of such drugs, or in outcome measures [520]. The review concluded that the available studies do not support the use of parasympathomimetics for treating UAB, especially when frequent and/or serious adverse effects (gastrointestinal upset, blurred vision, bronchospasm and bradycardia) are taken into account.

4.4.4.2.2 Alpha-adrenergic blockers

In order to improve bladder emptying, decreasing outlet resistance through sympathetic blockade at the bladder neck/urethra has been investigated. One prospective study with tamsulosin showed similar improvement in terms of uroflowmetry parameters (specifically in the percentage of patients who had a good therapeutic response) in women with BOO (39.4%) or DU (32.7%) [521]. Another longitudinal study including fourteen women with DU showed clinical and urodynamic improvements after tamsulosin [522]. A prospective single-blind RCT in female patients with DU compared efficacy of alpha-blocker, cholinergic drugs or combination therapy, with the latter exhibiting the best results [523].

4.4.4.2.3 Prostaglandins

Prostaglandins are prokinetic agents that promote smooth muscle contraction. Prostaglandins E2 and F2 have been used intravesically to treat urinary retention after surgery. A Cochrane review showed a significant association between intravesically administered prostaglandin and successful voiding among postoperative patients with urinary retention. However, the success rate was low (32%) compared to placebo. It should also be noted that the 95% CI was wide, RCTs included in the pooled analysis were underpowered with

methodological limitations, and the event rate was very low, indicating a very low certainty of the evidence [524]. Intravesical prostaglandin treatment is rarely used and further research is necessary before it can be taken up more widely.

4.4.4.3 Surgical management

4.4.4.3.1 Sacral nerve stimulation

Sacral nerve stimulation is approved by the US FDA for therapy of non-obstructive urinary retention. The mechanism of action has not been fully elucidated, but activation of afferent sensory pathways, modulation–activation of the central nervous system, and inhibition of inappropriate activation of the guarding reflex are some of the mechanisms proposed.

An RCT included 37 patients in the implantation arm and 31 in the standard medical therapy arm, showing a mean decrease in PVR volume in the implantation group compared with a control of 270 mL and a mean increase in voided PVR volume of 104 mL [525]. A meta-analysis of seven studies showed a mean difference in PVR volume reduction of 236 mL and a mean voided volume increase of 299 mL [526]. The response rate during the trial phase ranged from 33 to 90% (mean 54.2%) and the success rate of permanent implantation ranged from 55 to 100% (mean 73.9%), highlighting that patient selection is crucial [527]. A subgroup of women with idiopathic urinary retention (Fowler's syndrome) had a higher response rate of 68–77% [528].

In conclusion, SNS is a valid option for female patients with DU, with proper patient selection. Women should have preserved bladder contractility on urodynamic tests and mechanical/anatomical BOO should be excluded. Patients with evidence of anatomical BOO, suspected loss of intrinsic detrusor contractility or neurogenic bladder dysfunction show lower response rates [529].

4.4.4.3.2 Onabotulinumtoxin A

OnabotulinumtoxinA injections in external striated urethral sphincter may improve voiding in patients with DU by reducing outlet resistance and reducing the guarding reflex. Some retrospective case studies have shown improvement in voiding symptoms, recovery of spontaneous voiding, and improvement in urodynamic parameters (reduction of voiding pressure and/or urethral closure pressures, reduced PVR volume) [530, 531]. The duration of symptomatic relief is short; typically three months.

4.4.4.3.3 Transurethral incision of the bladder neck

Transurethral incision of the bladder neck has been described in short series of women with refractory DU. In a retrospective case study, 40/82 (48.8%) women achieved satisfactory outcomes (spontaneous voiding with voiding efficiency ≥ 50%), but five (6.1%) patients developed SUI and two (2.4%) developed a vesico-vaginal fistula [532].

4.4.4.3.4 Reduction cystoplasty

This is an uncommon procedure with a few case reports described only in men [533].

4.4.4.3.5 Myoplasty

One retrospective multicentre study reported the long-term results of latissimus dorsi detrusor myoplasty in patients with bladder acontractility, with 71% recovering complete spontaneous voiding, with a mean PVR volume of 25 mL [534]. No other groups have published their experience to reproduce these findings.

4.4.4.4 Summary of therapeutic evidence on detrusor underactivity

The level of evidence for most therapeutic interventions for DU is low. Only CISC remains as a gold standard to reduce the adverse consequences of a high PVR volume and incomplete voiding, in spite of the low level of evidence that supports this statement.

4.4.4.4.1 Summary of evidence and recommendations for underactive bladder

Summary of evidence	**LE**
Clean intermittent self-catheterisation has proven efficacy in patients who are unable to empty their bladder.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an enhanced risk of UTI.	3
Intravesical electrical stimulation may be useful in some patients after prolonged bladder over-distension.	3
Intra-urethral inserts/prostheses may be useful in selected patients as an alternative to CISC but existing research has highlighted issues with tolerance, infection and device migration.	2b

Parasympathomimetics do not improve clinical or urodynamic parameters of UAB and frequent and/or serious adverse effects may arise.	1b
There is limited evidence about effectiveness of alpha-adrenergic blockers in women with UAB.	2b
Very low certainty evidence indicates that intravesically administered prostaglandins may promote successful voiding in patients with urinary retention after surgery.	1a
Sacral nerve stimulation improves voided volume and decreases PVR volume in women with DU.	1b
There is limited evidence for the effectiveness of onabotulinumtoxinA external urethral sphincter injections to improve voiding in women with UAB.	3
Transurethral bladder neck incision may improve voiding in women with DU, but complications (SUI, vesico-vaginal fistulae) may appear.	3
There is limited evidence for effectiveness of detrusor myoplasty.	3

Recommendations	**Strength rating**
Encourage double voiding in those women who are unable to completely empty their bladder.	Weak
Warn women with underactive bladder (UAB) who use abdominal straining to improve emptying about pelvic organ prolapse risk.	Weak
Use clean intermittent self-catheterisation (CISC) as a standard treatment in patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of CISC.	Strong
Offer indwelling transurethral catheterisation and suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak
Do not routinely recommend intravesical electrical stimulation in women with UAB.	Weak
Do not routinely recommend parasympathomimetics for treatment of women with UAB.	Strong
Offer alpha-adrenergic blockers before more-invasive techniques.	Weak
Offer intravesical prostaglandins to women with urinary retention after surgery only in the context of well-regulated clinical trials.	Weak
Offer onabotulinumtoxin A external sphincter injections before more-invasive techniques as long as patients are informed that the evidence to support this treatment is of low quality.	Weak
Offer sacral nerve stimulation to women with UAB refractory to conservative treatment.	Strong
Do not routinely offer detrusor myoplasty as a treatment for detrusor underactivity.	Weak

*4.4.5 **Follow-up***

Natural history and clinical evolution at long-term follow-up of women with DU is not well known. No longitudinal cohort studies with long-term follow-up are described in the literature. The interval between follow-up visits depends on patient characteristics, treatments given and the frequency of urinary complications.

4.5 Bladder outlet obstruction

*4.5.1 **Introduction***

Bladder outlet obstruction is defined by the ICS as "*obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate*" [1]. Its precise diagnosis requires urodynamic evaluation including an assessment of pressure and flow.

Voiding dysfunction is a broad term defined by the ICS as *"a diagnosis made by symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or raised PVRs, ideally on repeated measurement to confirm abnormality"* [113]. Pressure–flow studies are required to determine the precise cause of the voiding dysfunction. In women, voiding dysfunction can be caused by BOO or DU [1]. There are also non-obstructive causes and therefore voiding dysfunction and BOO should not be used interchangeably. Another term that must be differentiated from BOO and voiding dysfunction is dysfunctional voiding, which is a specific and discrete form of voiding dysfunction characterised by an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated muscle during voiding in neurologically normal individuals [113].

*4.5.2 **Epidemiology, aetiology, pathophysiology***

4.5.2.1 Epidemiology

Estimates of prevalence of BOO among women vary from 2.7% to 29% [535]. One large series of women undergoing urodynamic evaluation for LUTS found that ~20% are diagnosed with BOO. The wide variance is due to several factors, including differences in definitions and diagnostic criteria for female BOO, differences in study populations, and variation in study methods. The estimated prevalence rates of LUTS due to BOO in women are lower than those reported in men (18.7–18.9% vs. 24.3–24.7%) [536].

Prevalence of voiding LUTS is associated with age [55, 537, 538], parity [55, 539], prolapse [55, 539] and prior continence surgery [55, 539]. Bladder outlet obstruction has long been postulated to cause mainly voiding symptoms [540] but recent data from a series of 1142 consecutive women referred for evaluation of LUTS suggest that storage symptoms may be predominant in women diagnosed with BOO, and excess daytime urinary frequency was the most common symptom reported by 69% [535].

4.5.2.2 Pathophysiology

Bladder outlet obstruction is one of multiple causes of voiding dysfunction in women. The obstruction can be either anatomical (mechanical) or functional. In anatomical BOO, there is a physical or mechanical obstruction to the outflow of urine, whereas in functional BOO there is a non-anatomical, non-neurogenic obstruction of the outlet usually resulting from non-relaxation of the bladder neck, sphincter or PFM, or increased urethral sphincter tone or PFM contraction during voiding, as observed in patients with dysfunctional voiding.

Mechanisms for anatomical (mechanical) obstruction include external compression, fibrosis, stricture or injury to the urethra and kinking of the urethra due to POP. Progressive fibroblastic reaction around the urethra induced by mesh tapes or slings used in incontinence surgery may also cause anatomical (mechanical) obstruction [495]. In a retrospective review of 192 women diagnosed with BOO, 64% had mechanical obstruction [535].

Functional obstruction may be caused by failure of relaxation, or contraction, of the bladder neck and/or urethral sphincter complex or the PFMs during sustained detrusor contraction [540]. The exact causes of this lack of relaxation, or contraction, are often elusive but might be due to sympathetic hyperactivity or hypertrophy of the bladder neck smooth muscle for primary bladder neck obstruction [541], or may be mostly behavioural for dysfunctional voiding [542].

4.5.2.3 Aetiology

Conditions associated with anatomical BOO include POP, incontinence surgery, urethral stricture, urethral stenosis, urethral diverticulum, urethral caruncle, urethral malignancies and paraurethral masses.

Conditions associated with functional BOO include primary bladder neck obstruction, dysfunctional voiding, and idiopathic urinary retention (Fowler's syndrome).

In primary bladder neck obstruction, the bladder neck fails to open adequately during voiding, in the absence of an anatomical obstruction [543]. It is estimated that 4.6–16% of women presenting with voiding symptoms have primary bladder neck obstruction [541].

Dysfunctional voiding is due to involuntary intermittent contractions of the periurethral striated or levator muscles during voiding in neurologically normal women, and is thought to be caused by faulty learned toileting behaviour [495]. There is also some evidence of a link between dysfunctional voiding and a history of sexual abuse [544].

Idiopathic urinary retention, also known as Fowler's syndrome, is a primary disorder of the external urethral sphincter with hypertrophy of the muscle fibres, which fail to relax during micturition. It is associated with decreased detrusor contractility via enhancement of the guarding reflex. It is seen most often, but not exclusively, in young women with urinary retention and is characterised by increased urinary sphincter volume and activity/tone, which may be hormonally triggered [545].

Alpha-adrenergic agonists, such as pseudoephedrine commonly contained in decongestants, can lead to some form of functional obstruction due to their stimulatory effects, which may contract the bladder neck and lead to urinary retention [546].

Neurological conditions can also bring about functional BOO in women. These conditions are not considered in these guidelines and are covered elsewhere [9].

*4.5.3 **Classification***

4.5.3.1 Anatomic bladder outlet obstruction

Anatomical BOO involves a physical or mechanical obstruction of the outflow of urine.

4.5.3.2 Functional bladder outlet obstruction

Functional BOO involves a non-anatomical, non-neurogenic obstruction of the outflow of urine resulting from non-relaxation or increased tone in the bladder neck and/or urethral sphincter complex or the PFMs (Table 5). Neurological causes of functional BOO are not considered in these guidelines and are covered elsewhere [9].

Table 5: Main causes of female bladder outlet obstruction

Functional BOO	Anatomical BOO
• Primary bladder neck obstruction • Dysfunctional voiding • Idiopathic urinary retention (Fowler's syndrome)	• Urethral stricture • Anti-incontinence surgery • Pelvic organ prolapse • Urethral diverticulum • Urethral caruncle • Urethral malignancies • Paraurethral masses

4.5.3.3 Recommendation for classification of bladder outlet obstruction

Recommendation	Strength rating
Use standardised classification of bladder outlet obstruction in women (anatomical or functional), and research populations should be fully characterised using such classification.	Strong

*4.5.4 **Diagnostic evaluation***

Diagnosis of BOO in women, although dependent on formal pressure–flow studies, may be suggested by several clinical and other non-invasive assessments.

4.5.4.1 Clinical history

In terms of clinical history, a range of LUTS may be elicited and these may not be confined to voiding LUTS. Women may not present until they have the possible complications of BOO, such as recurrent UTI, chronic urinary retention or acute/chronic kidney disease [535]. The evidence regarding clinical utility of symptoms for the diagnosis of BOO is inconclusive. In a single-centre retrospective study involving 587 women, 38 of whom were diagnosed with BOO, the authors concluded that symptom assessment alone was insufficient for diagnosis and a full urodynamic evaluation was essential [547]. A smaller retrospective study of 57 premenopausal women with bothersome LUTS found a significantly higher proportion of women with bladder dysfunction presenting with UUI. Patients with voiding phase dysfunction have higher total scores and voiding symptom subscores in the American Urological Association (AUA) symptom index [548]. Perhaps some of the difficulty in evaluating the diagnostic accuracy of urinary symptoms comes from the observation that a significant proportion of women presenting with obstruction also have concomitant urodynamic abnormalities. In a large study of > 5000 women with urinary symptoms including 163 with BOO, additional urodynamic diagnoses were noted in 54% [549]. Similarly, in a study involving 101 women with a primary diagnosis of SUI, the prevalence of BOO (based on maximum urine flow [Q_{max}] < 12 mL/s and maximum detrusor pressure at Q_{max} > 25 cm H_2O) was 16% [550]. Symptoms alone were not sufficient to discriminate between the various different diagnostic groups of women in these two studies. LUTS appear to be fairly sensitive to change following intervention for BOO. A prospective study in 53 women with clinically suspected voiding dysfunction describes significant symptom improvement in twelve of sixteen patients who underwent surgical intervention [551].

4.5.4.2 Clinical examination

There are no studies evaluating the clinical utility of physical examination in women with suspected BOO; nevertheless, it is widely considered as a key part of the medical assessment. It allows for visual inspection of the urethra and vagina for possible causes of mechanical obstruction as well as an assessment of the pelvic floor, which may be the cause of functional obstruction.

4.5.4.3 Uroflowmetry and post-void residual volume

Reduced Q_{max} and incomplete bladder emptying can result from weakness in the contractile strength of the detrusor muscle, or increased outlet resistance due to functional or anatomical/mechanical BOO. The use of uroflowmetry to differentiate between anatomical and functional BOO was explored in a retrospective study of 157 women [542], which concluded that Q_{max} was significantly lower in patients with anatomical obstruction, but a large degree of overlap was noted. The largest evaluation of the diagnostic utility of urine flow studies and PVR volume estimation was a retrospective analysis of > 1900 patients with symptoms of voiding dysfunction, of whom, > 800 were diagnosed with BOO based on urodynamic assessment [552]. Functional BOO was > 6 times more common than anatomical/mechanical obstruction, which does not agree with most of the other epidemiological literature for female BOO. The authors found that although urine flow rate alone was

not accurate enough to diagnose BOO, PVR of ≥ 200 mL could differentiate bladder neck dysfunction from the other causes of BOO, with a receiver-operator characteristics (ROC) area under the curve (AUC) of 0.69. Conversely, in a retrospective study involving 101 women primarily presenting with SUI, a good correlation between abnormal uroflowmetry and urodynamic obstruction (phi = 0.718, $p < 0.0001$) was found [550]. In a prospective study of > 50 women with a clinical diagnosis of voiding dysfunction, abnormal uroflow curves were observed in ~40% of women, but BOO based on pressure–flow results was confirmed in only 52% of these women [551].

4.5.4.4 Ultrasound

The major utility of US scanning in women with BOO is to detect possible complications such as bladder wall thickening or upper tract dilatation/hydronephrosis. However, the diagnostic capabilities of US have been investigated in a prospective case–control study of 27 patients with cystoscopically confirmed bladder neck obstruction [553]. The diagnostic value of shear wave elastography (SWE) and acoustic radiation force impulse imaging (ARFI) for female BOO was compared and the authors concluded that ARFI was more accurate than SWE, but a combination of the techniques was superior to both alone. Ultrasound scanning was further evaluated in a small study of fifteen women with BOO diagnosed urodynamically [554]. The authors proposed that transvaginal ultrasonography was able to demonstrate a closed bladder neck during attempts at micturition and concluded that this modality was useful for evaluation of the possible causal factors of female BOO, such as primary bladder neck obstruction.

4.5.4.5 Magnetic resonance imaging

The role of MRI in the diagnostic evaluation of female patients with suspected BOO is poorly defined. Although MRI allows for precise anatomical evaluation of pelvic structures, there are no reports of its clinical utility in the diagnosis of female BOO. Magnetic resonance imaging in patients with pathological urethral stricture can determine the degree of periurethral fibrosis, although the prognostic and clinical significance of such a finding has not been established [555].

4.5.4.6 Electromyography

Electromyography (EMG) has been most extensively studied in the subgroup of women with BOO due to idiopathic urinary retention caused by a high-tone non-relaxing sphincter (Fowler's syndrome). Abnormal urethral EMG activity may be associated with non-relaxation of the striated sphincter, abnormally high urethral pressure, and, through an exaggerated guarding reflex, poor bladder sensation and reduced detrusor contractile strength [544, 556]. Complex repetitive discharges and decelerating bursts are specific urethral EMG abnormalities that have been described in patients with high-tone non-relaxing sphincter, although these abnormalities have also been noted in asymptomatic volunteers [557, 558]. A review of voiding dysfunction in women included 65 studies with only a small number addressing the diagnostic utility of PFM EMG [495]. The authors commented that increased EMG activity of the PFM can be seen during voiding or non-relaxation, and when this is coupled with pressure–flow information from urodynamics, it may be useful to differentiate between functional and anatomical obstruction. Further evidence for this comes from a retrospective study of 157 women with roughly equal numbers of women with functional and anatomical obstruction, which concluded that a low level of PFM EMG activity is characteristic of anatomical obstruction [542]. Additional neurophysiological tests, such as anal sphincter EMG, bulbocavernosus reflex, and pudendal sensory evoked potentials can assess the integrity of the somatic S2–4 nerve roots; however, their clinical utility in the context of non-neurogenic female BOO needs to be better defined [544].

4.5.4.7 Cystourethroscopy

Cystourethroscopy can be useful to visualise any anatomical/mechanical obstruction and provide information regarding its nature, location and calibre. Given that pelvic malignancy may cause anatomical BOO, cystourethroscopy is considered an essential part of the diagnostic pathway. Formal urethral calibration may be useful for women with BOO secondary to pathological urethral stricture and various different urethral calibre thresholds have been used, from 14 to 20 Fr [559].

4.5.4.8 Urodynamics and video-urodynamics

Pressure–flow studies are the mainstay of BOO diagnosis and the characteristic abnormalities are a combination of low flow and concomitant high detrusor pressure [543]. However, while the general definition of BOO is well established, with some data supporting its clinical validity in male patients [560], the urodynamic definition of female BOO remains controversial [540]. Several urodynamic criteria have been introduced during the past twenty years but none has been established as a standard due to lack of clinical validation [540, 561]. The Blaivas and Groutz nomogram, which plots free Q_{max} and maximum detrusor pressure ($P_{det.max}$) measured during urodynamic studies, is one of the most popular [562] but has been suggested to overestimate

obstruction [563]. The addition of fluoroscopic imaging suggested by Nitti and colleagues introduces a video-urodynamic criterion for obstruction and has found popularity [77]. However, both methods lack data supporting their clinical validity, especially regarding their predictive value for therapeutic intervention outcomes [75].

In a large retrospective study of 1914 patients, 810 of whom were diagnosed with BOO, several urodynamic cut-off values were determined by ROC curve analysis to optimise the diagnostic accuracy of video-urodynamic studies [552]:

- $P_{det}Q_{max} \geq 30$ cm H_2O for differentiating BOO from bladder dysfunction and normal studies (ROC AUC = 0.78);
- the Abrams-Griffiths number > 30 for differentiating anatomical from functional BOO (ROC AUC = 0.66);
- $P_{det}Q_{max} \geq 30$ cm H_2O for differentiating dysfunctional voiding from poor relaxation of the external sphincter (ROC AUC = 0.93).

Other smaller studies with a similar methodology of utilising ROC curve analysis have concluded that neither pressure–flow data only, nor clinical symptoms alone, may be sufficient for diagnosing obstruction in women [564], therefore independent validation of any suggested thresholds is necessary.

More recently, Solomon and Greenwell devised a female BOO nomogram that parallels the ICS nomogram used for male BOO [565]. It allows the calculation of an alternative BOO female index (BOOIf), using a formula closely aligned to its male counterpart: $BOOIf = P_{det}Q_{max}\text{-}2.2Q_{max}$.

It is interpreted with a different algorithm however:

- BOOIf < 0: < 10% probability of obstruction;
- 5 < BOOIf < 18: equivocal, ≥ 50% likelihood of obstruction;
- BOOIf > 18: 90% likelihood of obstruction.

The Solomon–Greenwell nomogram was the first to be tested for clinical validity. In a recent series of 21 unselected consecutive women treated for BOO, the authors observed significant improvement of all urodynamic parameters (Q_{max}, $P_{det}Q_{max}$ and BOOIf) in female patients who became asymptomatic postoperatively [566].

An alternative urodynamic parameter of area under the detrusor pressure curve during voiding (corrected for voided volume) has been proposed following a prospective study of 103 women [567]. The authors concluded that this variable appears to be the most discriminating urodynamic parameter for the diagnosis of female BOO. This suggested diagnostic method has not been independently validated.

Voiding cystourethrography (VCUG) alone or in conjunction with concomitant pressure–flow studies may be useful in delineating the site of obstruction. Characteristic features include:

- radiographic evidence of obstruction between the bladder neck and distal urethra in the presence of
- sustained detrusor contraction [77];
- lack of funnelling appearance of the bladder neck/tight bladder neck in primary bladder neck obstruction;
- proximal dilatation of the urethra with distal narrowing in women with urethral stricture disease or pelvic-floor hypertonicity.

It is not uncommon for women with a voiding dysfunction, specifically functional BOO, to be unable to provide a flow during (video)urodynamic testing. Failure to relax the PFM can enhance the guarding reflex, limiting detrusor contractility.

4.5.4.9 Summary of evidence and recommendations for diagnosis of bladder outlet obstruction

Summary of evidence	**LE**
Evaluation of LUTS by history and examination alone is insufficient to accurately diagnose female BOO.	3
Urine flow studies cannot diagnose with high accuracy BOO in women.	3
Ultrasound scanning is unable to diagnose with high accuracy BOO in women.	2b
Electromyography alone is unable to diagnose with high accuracy BOO in women, although it may be of use in combination with pressure–flow studies and in differentiation of anatomical and functional BOO.	3
Urodynamics (often combined with video-fluoroscopy) is the standard test for evaluating female BOO.	3

Recommendations	Strength rating
Take a full clinical history and perform a thorough clinical examination in women with suspected bladder outlet obstruction (BOO).	Strong
Do not rely on measurements from urine flow studies alone to diagnose female BOO.	Strong
Perform cysto-urethroscopy in women with suspected anatomical BOO.	Strong
Perform urodynamic evaluation in women with suspected BOO.	Strong

*4.5.5 **Disease management***

Therapeutic interventions for BOO aim to decrease outlet resistance in order to increase urinary flow, improve bladder emptying and thus reduce voiding and storage LUTS [75, 540, 561]. Treatment choice is commonly dictated by the nature of the underlying cause of the obstruction.

4.5.5.1 Conservative management

4.5.5.1.1 Behavioural modification

Behavioural modification aims to improve or correct maladaptive voiding patterns through analysis and alteration of the relationship between the patients' symptoms and their environment, lifestyle and habits. Behavioural modification interventions are often tailored to individual patients' needs, symptoms and circumstances and can include elements such as education regarding normal voiding function, self-monitoring of symptoms, changes in lifestyle factors that may affect symptoms, avoidance of constipation, and alteration of voiding technique. Ultimately, techniques aim to improve the coordination between the detrusor and sphincter, resulting in their synergistic action [75, 540, 561].

The vast majority of individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. General interventions such as those listed above may help with symptoms resulting from BOO but no quantification of their effect is possible.

4.5.5.1.2 Pelvic floor muscle training +/- biofeedback

Pelvic floor muscle training aims to improve pelvic floor function and urethral stability. In the context of BOO, physiotherapy aims to teach patients to relax their PFMs and striated urethral sphincter during voiding. Pelvic floor muscle contraction, particularly in women with pelvic floor dysfunction, has been shown to significantly reduce vaginal resting pressure and surface EMG activity [514]. A twelve-week PFMT programme in postmenopausal women demonstrated significant improvement in the speed of relaxation after PFM contraction and a decrease in PFM tone [515].

As mentioned in the section discussing UAB (Section 4.4.4.1.2), most of the evidence supporting PFMT in dysfunctional voiding is from paediatric studies.

A case-series reported improved PFM relaxation and voiding function following PFMT with biofeedback in fifteen women with dysfunctional voiding based on a dilated proximal urethra on voiding cysto-urethrography and hyperactivity of the pelvic muscles or external urethral sphincter on EMG during voiding. No clinical outcomes were reported by this series [568].

4.5.5.1.3 Electrical stimulation

Application of electrodes that allow for controlled contraction and relaxation of the PFMs may theoretically facilitate the relaxation of the external sphincter and pelvic floor but no critical evaluation of this intervention in women with BOO has been published.

4.5.5.1.4 Use of vaginal pessary

Intravaginal devices such as pessaries aim to relieve voiding symptoms and improve bladder emptying by physical correction of the obstruction caused by a POP. In a prospective study of eighteen women with grade three or four cystocoeles and diagnosed with BOO by urodynamics (defined as $P_{det}Q_{max}$ > 25 cm H_2O, Q_{max} < 15 mL/s), normal voiding was noted in seventeen (94%) immediately after placement of a vaginal pessary. No other outcomes were available in this series [569]. No long-term data are available on the use of vaginal pessary for BOO.

4.5.5.1.5 Urinary containment

Urinary containment devices include body-worn absorbent products. Their use in BOO is to achieve social continence in patients with urinary retention and associated overflow UI and they are often only a temporary measure. There are no published studies on the outcomes or adverse events associated with the use of urinary containment devices for the management of female BOO. While there may be no studies exclusively involving women with BOO, there are many involving women with UI who may have BOO as an underlying cause.

4.5.5.1.6 Urinary catheterisation

Significant urinary retention from BOO may be addressed by actively bypassing the obstruction and draining the residual urine. Catheterisation may be used as a treatment itself or as an adjunct to an initial treatment of urethral dilatation or urethrotomy or bladder neck incision. There are two ways of using a catheter: CISC or indwelling catheterisation [116].

After UI surgery, BOO may be managed by short-term catheterisation in most patients who have transient postoperative voiding difficulty. For a few women who develop chronic urinary retention, CISC or indwelling catheterisation may be offered [495].

A small RCT investigated the effectiveness of CISC to prevent recurrence after internal optical urethrotomy for urethral stricture disease. In the treatment group, CISC was done twice a day for one week, and once a day for four weeks, then once weekly for seven weeks post-urethrotomy. Freedom from stricture recurrence, determined by urethrography and uroflowmetry performed twelve weeks postoperatively, was higher in the catheterisation group compared to the group with no catheterisation (78.5% vs. 55.4%) [570]. This finding mirrors the Cochrane review on self-dilatation for urethral stricture among men that showed less recurrence with the performance of self-dilatation [571].

In a series of 20 patients with voiding dysfunction after TVT who were put on a CISC programme, overall cure rate was 59%, with cure defined as consistent residual volume < 100 mL. Half of these patients were voiding normally within twelve weeks [572].

A patient satisfaction survey involving 188 patients on CISC/self-dilatation, which included 38 patients with urethral stricture, showed positive (pleased or satisfied) outcomes in 54.3% of patients, while 28.2% had mixed feelings and 9.6% were unhappy. No rates were given specifically for the BOO group [573].

4.5.5.1.7 Intraurethral inserts

An intraurethral insert is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. The valve-pump mechanism is operated by an external control unit, which activates to open the valve and the pump to draw urine from the bladder and allow voiding. At the end of urination, the pump ceases to rotate and the valve closes to regain continence. The insert is routinely replaced once a month.

Only one study reported the use of this device in 92 women with voiding dysfunction of various aetiologies including multiple sclerosis, prior pelvic surgery, pelvic radiation, diabetes mellitus, and spinal stenosis and injury. The device was removed within seven days of insertion in 60% of the cases due to discomfort, pericatheter leakage or technical difficulty. An additional 20% of patients had late discontinuation. All those who continued to use the device were satisfied, with PVR volumes remaining < 100 mL. Adverse events included migration into the bladder in six cases and symptomatic UTI in four cases [574, 575]. Extended, long-term data on the use of urethral inserts are not available.

4.5.5.1.8 Extracorporeal magnetic stimulation

Extracorporeal magnetic stimulation involves the patient sitting on a device that induces consistent PFM contraction and relaxation by repeated magnetic stimulation of motor nerve fibres. Extracorporeal magnetic stimulation contracts and then relaxes the PFM following a set frequency and interval. It is postulated that patients could therefore learn to spontaneously contract or relax the PFM, which may enhance their ability to relax their pelvic floor while voiding [576].

In a small (n = 60) prospective non-randomised trial, alfuzosin was compared to EMS and to the combination of alfuzosin + EMS in women with functional BOO. They observed significant increase of Q_{max} and significant decrease of International Prostate Symptom Score (IPSS) in all groups and significantly greater improvement in the QoL question of the IPSS in the combination therapy group [576].

4.5.5.1.9 Summary of evidence and recommendations for conservative treatment of bladder outlet obstruction

Summary of evidence	**LE**
Pelvic floor muscle relaxation training with biofeedback may result in relaxation of the pelvic muscles and external urethra in women with dysfunctional voiding.	3
There is no available evidence in the published literature on the clinical effect of ES for management of female BOO.	NA

In women with large (grade three or four) cystocoeles causing bladder outlet obstruction (BOO), placement of a vaginal pessary may improve voiding efficiency.	3
Regular CISC after urethrotomy is better than no catheterisation to prevent recurrence of urethral strictures.	1b
A CISC programme in women with voiding dysfunction after TVT has a cure rate of 59%.	3
Women who use an intraurethral device have lower PVR volume but most require its removal due to complications.	3
Extracorporeal magnetic stimulation combined with alfuzosin may be more effective than either of these therapies alone in women with functional BOO.	2a

Recommendations	Strength rating
Offer pelvic floor muscle training (PFMT) aimed at pelvic floor muscle relaxation to women with functional bladder outlet obstruction (BOO).	Weak
Prioritise research that investigates and advances understanding of the mechanisms and impact of PFMT on the coordinated relaxation of the pelvic floor during voiding.	Strong
Offer the use of a vaginal pessary to women with grade three or four cystocoeles and BOO who are not eligible/inclined towards other treatment options.	Weak
Offer urinary containment devices to women with BOO to address urinary leakage as a result of BOO, but not as a treatment to correct the condition.	Weak
Offer clean intermittent self-catheterisation to women with urethral strictures or post-urinary incontinence surgery for BOO.	Weak
Do not offer an intraurethral device to women with BOO.	Strong

*4.5.6 **Pharmacological management***

4.5.6.1 Alpha-adrenergic blockers

Alpha-adrenergic blockers are postulated to relieve LUTS caused by BOO in women via smooth muscle relaxation in the bladder neck, thus decreasing bladder outlet resistance [577].

Systematic reviews on the use of alpha-blockers in women generally involve studies with a population that includes women complaining of LUTS and voiding dysfunction. Confirmation of BOO is often not required in the trials included [578, 579]. These reviews showed significant improvements in symptoms and urodynamic parameters associated with their use [578-580]. A meta-analysis of fourteen RCTs comparing alpha-blockers and placebo in women with LUTS showed significant symptom relief after alpha-blocker treatment relative to placebo, but no significant difference in Q_{max}, PVR and adverse event rates [578]. This is in contrast to prospective non-comparative trials that consistently showed improvements in voiding and storage symptoms, bother scores, and urodynamic parameters [Q_{max}, PVR, $P_{det}Q_{max}$, MUCP after alpha-blocker use compared to baseline [521, 522, 581-583].

A SR performed by the Panel of studies on alpha-blockers used specifically for women with BOO included one placebo-controlled RCT, one RCT comparing two types of alpha-blockers, and six prospective non-comparative studies. In the only placebo-controlled RCT reporting subgroup analyses in women with urodynamically proven BOO (based on the Bladder and Groutz nomogram) no significant difference was observed in the changes of IPSS, IPSS sub scores, Q_{max}, PVR volume and bladder diary after eight weeks of alfuzosin (n = 58) vs. placebo (n = 59). Of note, no EMG and/or voiding cysto-urethrography was used to distinguish between dysfunctional voiding and primary bladder neck obstruction [584].

Information on the comparative effectiveness of the different types of alpha-blockers was limited to one RCT. A small trial of 37 women with IPSS > 8, Q_{max} < 12 mL/s and PVR volume > 50 mL, compared tamsulosin and prazosin over a three-month treatment period. More patients treated with tamsulosin were completely satisfied with their treatment (16/20 vs. 9/20). Both treatment groups showed significant improvement in symptom scores from baseline but no further statistical comparison between the groups was done. However, a larger decrease in the AUA Symptom Index was seen in the tamsulosin group compared with the prazosin group. More adverse events were reported with prazosin (thirteen vs. one case) [585].

A small three-arm non-RCT in women with functional BOO compared alfuzosin monotherapy and EMS. The combination of alfuzosin and EMS showed greater improvement in storage symptoms and QoL than alfuzosin monotherapy alone [576].

4.5.6.2 Striated muscle relaxants

Baclofen is a gamma-aminobutyric acid (GABA) agonist that exerts its effect on the GABAergic interneurons in

the sacral inter-mediolateral cell column responsible for the relaxation of the striated urinary sphincter during voiding. Intrathecal administration has been shown to improve voiding in a trial among patients with spinal cord injury. Oral baclofen has also been widely studied [561].

A randomised placebo-controlled crossover trial investigated the efficacy and safety of a four-week course of oral baclofen 10 mg three times/day in 60 women diagnosed with BOO, based on increased EMG activity with sustained detrusor contraction during voiding. It showed a lower number of voids, significant improvements in Q_{max} and $P_{det}Q_{max}$ with baclofen compared with placebo. Post-void residual volume, maximum cystometric capacity and MUCP were not significantly different between the groups. Adverse event rates were also similar, with the most common being somnolence, dizziness and nausea. An important limitation of this study was the lack of patient-reported outcomes to assess symptoms and QoL [586].

A small case series reported the outcomes of 20 women with functional BOO who were given oral baclofen 5 mg three times/day for twelve weeks. There was significant improvement in the mean voided volume and BVE. However, Q_{max}, $P_{det}Q_{max}$, PVR volume and urethral profile pressures did not significantly change. No significant adverse events were noted [587].

4.5.6.3 Oestrogens

The relative reduction in urethral wall compliance seen in atrophic urethritis due to oestrogen deprivation may be responsible for urethral obstruction in postmenopausal women. Oestrogen therapy is thus theoretically expected to improve the condition. There are no published studies on the use of oestrogens specifically for the management of female BOO.

4.5.6.4 Sildenafil

Sildenafil, by inhibiting phosphodiesterase 5, increases the levels of nitric oxide in the female urethral sphincter, thereby promoting urethral relaxation.

A placebo-controlled, randomised crossover trial that included twenty women with partial or complete retention or obstructive voiding, with high MUCP and elevated US-estimated sphincter volume (> 1.6 cm) showed that while there was significant improvement in symptom scores and urodynamic parameters from baseline with sildenafil treatment, this difference was not significant when compared with placebo [588].

4.5.6.5 Thyrotropin-releasing hormone

Intravenous thyrotropin-releasing hormone (TRH) has been postulated as a neurotransmitter that induces urethral relaxation [589]. The exact mechanism is unclear.

In a small RCT of sixteen women with voiding difficulty, eight (three with BOO) were randomised to receive 200 µg intravenous bolus of TRH, and eight (three with BOO) received saline. No difference in the decline in functional profile lengths and maximum urethral closure pressures were noted between treatment groups, despite a significant decline noted from baseline in the treatment group. No subgroup analysis of women with BOO was reported [589].

4.5.6.6 Summary of evidence and recommendations for pharmacological management

Summary of evidence	**LE**
Alpha-adrenergic blockers are associated with significant improvement in symptom scores from baseline, but not urodynamic parameters compared with placebo.	1a
Tamsulosin is associated with greater improvement in symptom score compared with prazosin.	1b
Non-specific alpha-blockers are associated with higher rates of adverse events.	1b
Oral baclofen is better than placebo in improving Q_{max} and $P_{det}Q_{max}$, but not other urodynamic parameters. Its effects on symptoms are not well reported.	1b
Current evidence does not show that sildenafil is superior to placebo in improving symptoms or urodynamic parameters of female patients with BOO.	1b
Trials including women with voiding problems of mixed aetiologies showed no difference in urodynamic outcomes between intravenous TRH and placebo.	1b

Recommendations	**Strength rating**
Offer uroselective alpha-blockers, as an off-label option, to women with functional bladder outlet obstruction (BOO) following discussion of the potential benefits and adverse events.	Weak

Offer oral baclofen to women with BOO, particularly those with increased electromyography activity and sustained detrusor contraction during voiding.	Weak
Only offer sildenafil to women with BOO as part of a well-regulated clinical trial.	Strong
Do not offer thyrotropin-releasing hormone to women with BOO.	Strong

*4.5.7 **Surgical management***

4.5.7.1 Intra-sphincteric botulinum toxin injection

Botulinum toxin inhibits the presynaptic release of acetylcholine, which reduces urethral sphincter tone. It is also believed to decrease the release of noradrenaline in the urethra to counteract external urethral sphincter overactivity [590].

Evidence on the use of botulinum toxin for female BOO is limited to small case series. Most studies included mixed populations without subgroup analyses, or the diagnosis of voiding dysfunction could not be ascertained as solely resulting from BOO. No comparative trial exclusively involving female BOO patients using botulinum toxin has been identified in the literature.

A SR including several reports of small case series using variable doses of botulinum toxin A injected periurethrally in women with dysfunctional voiding showed improvements in symptoms, and reductions in residual volume and voiding detrusor pressure. Larger series in adults (both sexes) showed success rates of 86–100% [590].

A double-blind, placebo-controlled RCT (n = 73) 100 U onabotulinumtoxinA vs. saline resulted in significantly lower IPSS score and larger voided volume compared with saline in 31 men and women with dysfunctional voiding. Dysfunctional voiding was defined by a spinning top appearance on real-time fluoroscopy, poorly relaxed urethral sphincter on EMG, and a normal-to-high voiding pressure with a low and/or intermittent urinary flow rate, a PVR volume > 300 mL, and a low voiding efficiency. Other urodynamic parameters were comparable between the groups [591]. A subgroup analysis on the female population of this study was not available.

Two small case series in women with BOO reported the effects of 100 U intra-sphincteric injection of BTA. Both showed improvement in symptom and bother scores and significant reduction in PVR volume [544, 592]. One study reported increased Q_{max} and improved static urethral pressure profile (UPP) [544]. The average symptom-free duration was 16.8 weeks in another study [592]. Adverse events included UTI and temporary need for CISC. No SUI was reported.

4.5.7.2 Sacral nerve stimulation

Sacral nerve stimulation is a type of neuromodulation that allows continuous ES from an electrode placed alongside the sacral nerve via a surgically implanted pulse generator. Electrical stimulation is postulated to decrease urethral tone. Sacral nerve stimulation is also postulated to work by blockade of the inhibitory urethral afferent impulses, which cause inhibition of normal bladder contraction.

No comparative trial as been identified in the literature on the use of neuromodulation for female BOO.

Most publications on neuromodulation for voiding dysfunction are retrospective reviews of cases, involving a mix of patient populations who underwent the procedure for different indications. In studies that indicated a subgroup of patients with urinary retention, there was either no urodynamic confirmation of the nature of the retention or separate outcomes were not reported for participants with retention.

A review of 60 women who underwent for urinary retention associated with outlet obstruction (defined as UPP > 100 cm H_2O, increased urethral sphincter volume > 1.8 mL, and abnormal EMG with repetitive discharges and decelerating bursts) showed an overall spontaneous voiding rate of 72% over a mean follow-up of four years. Of those who continued to require CISC up to twice daily postoperatively, the frequency was less than prior to surgery (degree not specified). There were 99 adverse events and 63 surgical revisions. In this series, half of the patients underwent a one-stage SNS procedure and the other half a two-stage procedure. The proportion of patients who required CISC-assisted voiding was higher in the two-stage group (27% vs. 17%). More serious adverse events (defined as events requiring admission or surgical revision to resolve issues such as loss of response, lead migration and surgical revisions) were associated with the one-stage procedure [588].

In a single-centre series in a subgroup of 32 patients diagnosed with idiopathic urinary retention (Fowler's syndrome) who underwent SNS, 62.5% achieved a > 50% reduction in CISC rate [593].

4.5.7.3 *Pelvic organ prolapse surgery*

Pelvic organ prolapse surgery may relieve BOO by correcting the urethral kinking caused by the prolapse or by relieving the urethral compression brought about by the prolapsing organ [75, 540, 561].

Bladder output obstruction due to POP may be addressed by corrective surgery. Based on reviews, the majority of patients who had BOO caused by POP who had repair of their cystocoele demonstrated improvement of their voiding difficulties [495, 594].

A multicentre prospective study involving 277 women with at least grade two symptomatic POP who underwent surgery demonstrated a significant reduction in voiding symptoms and PVR volume one year postoperatively [595].

A retrospective study of 50 women who underwent laparoscopic sacrocolpopexy for POP showed a significant increase in mean postoperative Q_{max} and decrease in $P_{det}Q_{max}$ and PVR in those aged ≥ 65 years. The OAB symptom score improved but there was no significant difference in the ICIQ-SF score postoperatively [596].

In a case series of 35 women with stage III or IV POP presenting with a preoperative PVR volume > 100 mL (mean 226 mL), 89% had PVR volume < 100 mL postoperatively [597]. In another case series of 39 patients with cystocoeles who complained of voiding symptoms preoperatively, 30 (79%) achieved normal voiding, defined as no obstructive symptoms and a PVR volume < 50 mL, after bladder neck suspension with anterior colporrhaphy [598].

4.5.7.4 *Urethral dilatation*

Urethral dilation involves the passage of sequentially greater diameter dilators into the urethra, causing the obstructing fibrotic tissue to break open, thereby widening the lumen. It is considered the primary procedure of choice for women suspected of urethral stricture disease [559]. Dilation of up to 30–40 Fr has been done. There is no standard dilatation technique; dilatation of up to 43 Fr has been described, although other authors suggest dilating to 30 or 35 Fr.

A SR of female urethral stricture management included three trials involving urethral dilatation. Pooled analysis of data from 93 women showed a mean success rate of 49% after urethral dilation to 41 Fr with a mean follow-up of 46 months. Mean time to failure was twelve months. In treatment-naïve patients, success rate (as defined by trialists) was 58%, compared with 27.2% in patients who had undergone previous dilatation [555].

An RCT of 50 women with OAB syndrome and associated urodynamically confirmed BOO (defined as a Q_{max} < 15 mL/s with a voided volume of ≥ 100 mL and/or PVR volume > 200 mL, not due to urethral stricture) compared the effect of cystoscopy and bladder distension with urethral dilatation (n=22) and cystoscopy only (n=28) after six weeks' follow-up. Significantly more patients who had cystoscopy only had persistent urgency at six weeks and six months postoperatively. Urodynamic parameters did not significantly change pre- and postoperatively in both groups. The greater improvement in QoL scores based on the King's Health Questionnaire domain scores seen in the non-urethral dilatation group in this trial should be interpreted cautiously because of the higher baseline scores. There were no significant changes in Q_{max}, PVR volume, voided volume or $P_{det}Q_{max}$ in any of the two groups at six weeks' questioning of the role of any of these two options for therapeutic management of BOO. Also, six patients (12%) developed postoperative SUI [599].

A prospective trial of 86 women with primary urethral stricture compared on-demand vs. intermittent urethral dilatation to 24 Fr (dilate every two months). It showed an overall increase in Q_{max} and decrease in PVR volume post-dilatation. Significantly greater improvements were seen in the intermittent urethral dilatation group [600].

Three small case series showed improvements in symptoms with relief of urgency and/or UUI but inconsistent results in terms of significant improvement in Q_{max}, PVR volume and $P_{det}Q_{max}$. Benefits were poorly sustained, with most patients requiring additional or repeat intervention in the long-term [601-603].

Worsening or new-onset SUI is a concern with urethral dilatation but it is less of a concern than after urethrotomy or surgical reconstruction. Patients have also reported frequency and urgency post-dilatation [603].

4.5.7.5 *Urethrotomy*

Urethrotomy involves incision of the urethra endoscopically or using a urethrotome. It addresses the urethral narrowing by cutting open the scar tissue which is causing the obstruction [75, 540, 561, 603].

A prospective study of ten women with urethral strictures investigated the effect of Otis urethrotomy to 40 Fr followed by six weekly dilatations. There was significant improvement in IPSS, QoL, voided volume, Q_{max} and PVR volume at six months. Only the improvements in PVR volume and QoL were maintained on long-term follow-up (mean 82 months) [601].

4.5.7.6 Bladder neck incision/resection

Transurethral bladder neck incision decreases resistance at the bladder neck by cutting open the hypertrophic bladder neck smooth muscle in patients with primary bladder neck obstruction. Transurethral incision of the bladder neck may be performed with a unilateral incision at the twelve o'clock position or with bilateral incisions at the five and seven o'clock, two and ten o'clock or three and nine o'clock positions, or four incisions at the three, six, nine and twelve o'clock positions. This may be done using a resectoscope with a Collin's knife, cold knife, or using laser energy. Some authors report additional resection of the bladder neck between the five and seven o'clock positions during the procedure.

Evidence on bladder neck incision or resection for female BOO is limited to non-comparative trials. A review of studies on bladder neck incision for the treatment of bladder neck obstruction in women reports success rates of 76–100% [543].

Bladder neck incision was compared with V-Y-reconstruction using Nesbit's technique in a retrospective study of seventeen women with BOO, diagnosed by various uroradiological, endoscopic and urodynamic investigations. The results showed similar symptomatic improvement rates and postoperative PVR volume between the two groups. V-Y plasty had a longer operating and catheter time, lower uroradiological improvement rate, higher transfusion rate, and higher adverse event rate [604].

Several prospective case series consistently reported significant improvements in IPSS, QoL, Q_{max}, $P_{det}Q_{max}$ and PVR volume after treatment compared to baseline, regardless of the site of the incision, type of energy used or the length of follow-up [605-608].

The largest case series with 84 patients diagnosed with primary bladder neck obstruction (based on lack of funnel shape of the bladder neck during voiding on voiding cysto-urethrography, $P_{det} > 20$ cm H_2O and $Q_{max} < 12$ mL/s) showed success in 84.5% of patients with improvement in IPSS, QoL, Q_{max} and $P_{det}Q_{max}$ after mean follow-up of 27.4 months (6–78 months). Complications included vesico-vaginal fistula (VVF) (3.6%), SUI (4.7%) and urethral stricture (3.6%) [605].

No comparisons have been made between the different incision techniques (location, length and depth of incision, implement used – cold knife vs. hot knife vs. laser, with or without resection). However, in a case series of 84 patients, complications of VVF and SUI were noted in the cohort of patients who had their incisions at two and ten o'clock positions, and not in those who had their incisions at two and ten o'clock [605].

Adverse events include SUI, requirement for reoperation, and recurrence. Postoperative SUI was reported in 3– 33% [543].

4.5.7.7 Urethroplasty/urethral reconstruction

Surgical reconstruction of the female urethra has been used in the management of extensive urethral stricture. Several urethroplasty techniques have been reported including the use of vaginal or labial flaps, as well as vaginal and buccal grafts after cutting open the fibrotic tissue causing the urethral obstruction [609]. The use of bladder flaps has also been reported [610], and laboratory-engineered tissue grafts have also been used [610].

The surgical approaches have been described based on the position relative to the urethra; dorsal, ventral or circumferential. The dorsal approach is believed to provide better mechanical support and a more vascularised bed for a graft or flap. However, there is greater risk of damage to the sphincter and clitoral bodies with this approach. The ventral approach is more familiar to most surgeons and requires less urethral mobilisation. However, it is reported as being more prone to urethrovaginal fistulae, although it is not clear to what extent [559].

Reviews of studies reporting outcomes of urethroplasty state success rates of 57–100% [611]. Pooled analysis from six studies using vaginal or labial flaps showed a mean success rate of 91% with a mean follow-up of 32 months. Vaginal or labial graft urethroplasty was reported to have an 80% success rate with a mean follow-up of 22 months.

Oral mucosal grafts, reported in seven studies, had a mean success of 94% after a mean follow-up of fifteen months [559]. A later review of studies on dorsal buccal mucosal graft reported success rates of 62–100%, with a pooled success rate of 86% [612]. A long-term study with a mean follow-up of 32 months showed a stricture recurrence rate of 23.1% [611].

A retrospective comparative study of ten women who underwent urethral dilatation and twelve who underwent dorsal onlay pedicled labial flap urethroplasty, reported significant improvements in both groups in QoL, AUA Symptom Index, PVR volume and Q_{max}. The urethroplasty group had significantly better QoL scores and Q_{max} (17.0 vs. 12) at follow-up compared with the dilatation group [613]. Adverse events associated with urethroplasty include new-onset SUI and urgency and worsening of UUI.

4.5.7.8 Urethrolysis

Bladder outlet obstruction in women occurring as a complication of surgery for SUI may be managed surgically by urethrolysis, to regain urethral mobility. Urethrolysis may involve removal of periurethral anti-incontinence sutures, scar tissue and fibrosis.

Case series showed success rates measured as improved voiding and lower residual volumes, improvement or resolution of symptoms and QoL, and improvement of urodynamic parameters after treatment [614-616]. *De novo* SUI was reported in 39% in one study [616].

A study on 21 patients who underwent urethrolysis suggested an association of persistent postoperative bladder symptoms with greater delay in performing urethrolysis. Patients who presented with postoperative storage and voiding symptoms after a mean seventeen months' follow-up had a longer time to urethrolysis compared to those who had no complaints (31 vs. nine months) [617].

4.5.7.9 Removal/excision/section/loosening of mid-urethral sling

In women who develop BOO after placement of a mid-urethral sling, surgical management may include tape loosening, incision or division, and excision and/or removal of the tape [495].

Several small retrospective reviews of cases using different techniques of sling revision (incision, partial excision, or excision) showed good success rates in terms of symptom reduction, resumption of voiding with significant reduction in PVR volume and improvement of urodynamic parameters. Stress urinary incontinence recurs in a small proportion of patients and often to a lesser degree than prior to the sling procedure. Studies have shown long-term efficacy, including preservation of continence.

In a series of 63 women who presented with voiding dysfunction and persistent PVR volume > 100 mL after tape surgery for UI, different techniques were compared. Comparisons involved sling revision: sling division (n = 46) vs. partial sling excision (n = 13) vs. sling revision (division or excision) with an additional anti-SUI procedure (n = 4). The authors reported an overall success rate of 87% (PVR volume < 150 mL). No significant difference in success rates was demonstrated among the different revision techniques. There was a greater need for surgery for recurrent SUI in the partial sling excision group without an anti-SUI procedure (23% vs. 2.2 and 0) [618].

4.5.7.9.1 Timing of sling revision

One study showed that patients who underwent surgical release > 180 days after initial anti-UI surgery had significantly less recurrent SUI compared with patients who underwent the release sooner (15% vs. 46%) [619].

4.5.7.10 Summary of evidence and recommendations for surgical management of bladder outlet obstruction

Summary of evidence	**LE**
Intrasphincteric injection of botulinum toxin results in the improvement of symptoms and urodynamic parameters.	2
Sacral nerve stimulation results in spontaneous voiding and a reduction in CISC rate in the majority of female BOO patients in idiopathic urinary retention.	3
More serious adverse events and surgical revisions were associated with the one-stage neuromodulator implantation procedure.	3
Repair of POP improved PVR and voiding symptoms.	3
Urethral dilatation in women with BOO results in significant improvement in OAB symptoms, but improvements in urodynamic parameters of voiding are inconsistent.	1b

Programmed intermittent urethral dilatation results in better outcomes compared with on-demand dilatation.	3
Effects of urethral dilation are poorly sustained, requiring repeat intervention in the long term.	3
Internal urethrotomy followed by regular dilatations resulted in significant improvement in symptoms and urodynamic parameters in women with BOO.	3
Bladder neck incision in females with BOO results in improvements in symptoms and urodynamic parameters.	3
Complications of bladder neck incision are not common, but include VVF, SUI, and urethral stricture.	3
Urethroplasty using grafts or flaps in women with BOO due to urethral stricture have good success rates with significant improvements of symptoms, QoL scores and urodynamic parameters compared to baseline.	3
Urethroplasty results in better QoL and Q_{max} compared to urethral dilatation.	2
Long-term results showed significant stricture recurrence rate after urethroplasty.	3
Urethrolysis performed on women with voiding problems after anti-UI surgery resulted in improvements in symptoms, QoL and urodynamic parameters post-operatively.	3
Delayed urethrolysis was associated with persistent post-operative bladder symptoms.	3
Sling revision in women who presented with urinary retention or voiding problems and significant PVRs after sling surgery for UI resulted in improvements in symptoms and urodynamic parameters, resumption of voiding and reductions in PVRs.	3
Sling revision is associated with the risk of recurrent SUI.	3

Recommendations	**Strength rating**
Offer intra-sphincteric injection of botulinum toxin to women with functional bladder outlet obstruction (BOO).	Weak
Offer sacral neuromodulation to women with functional BOO.	Weak
Advise women with voiding symptoms associated with pelvic organ prolapse that symptoms may improve after surgery.	Weak
Offer urethral dilatation to women with urethral stenosis causing BOO, but advise on the likely need for repeated intervention.	Weak
Offer internal urethrotomy with postoperative urethral self-dilatation to women with BOO due to urethral stricture disease but advise on its limited long-term improvement and the risk of postoperative urinary incontinence (UI).	Weak
Do not offer urethral dilatation or urethrotomy as a treatment for BOO to women who have previously undergone mid-urethral synthetic tape insertion due to the theoretical risk of causing urethral mesh extrusion.	Weak
Inform women of limited long-term improvement (only in terms of post-void residual volume and quality of life) after internal urethrotomy.	Weak
Offer bladder neck incision to women with BOO secondary to primary bladder neck obstruction.	Weak
Advise women who undergo bladder neck incision on the small risk of developing stress urinary incontinence (SUI), vesico-vaginal fistula or urethral stricture postoperatively.	Strong
Offer urethroplasty to women with BOO due to recurrent urethral stricture after failed primary treatment.	Weak
Caution women on the possible recurrence of strictures on long-term follow-up after urethroplasty.	Weak
Offer urethrolysis to women who have voiding difficulties after anti-UI surgery.	Weak
Offer sling revision (release, incision, partial excision, or excision) to women who develop urinary retention or significant voiding difficulty after tape surgery for UI.	Strong
Caution women about the risk for recurrent SUI and the need for a repeat/concurrent anti-UI surgery after sling revision.	Strong

*4.5.8 **Follow up***

Women with BOO should be followed up and monitored regularly due to the risk of further deterioration of voiding or renal function in case of persistence and progression of the obstruction. For those who received treatment, monitoring must be done for recurrence of BOO. In particular, women who undergo urethral dilation, urethrotomy or urethroplasty for urethral stricture need to be monitored for stricture recurrence.

4.6 Nocturia

Nocturia was defined by the ICS in 2002 as *"the complaint that the individual has to wake at night one or more times to void"* and quantified in an updated document in 2019 as *"the number of times an individual passes urine during their main sleep period, from the time they have fallen asleep up to the intention to rise from that period"* [620]. The EAU Guidelines Panel on Urinary Incontinence conducted a SR on nocturia in women (596). The search covered evidence up to 2017 and this review was updated with a scoping search in 2020.

*4.6.1 **Epidemiology, aetiology, pathophysiology***

The prevalence of nocturia varies according to age with 4–18% of women aged 20–40 years experiencing ≥ 2 episodes per night, compared to 28–62% of women aged ≥ 70 years [621]. In a study of 1000 community-dwelling older adults, female nocturia was associated with older age, African–American race, history of UI, lower limb oedema and hypertension [622]. A report on > 5000 adults aged 30–79 years identified around 28% with nocturia and found additional correlates with increased BMI, cardiac disease, type 2 diabetes and diuretic use [623]. A SR and meta-analysis with moderate certainity evidence based on the GRADE approach, demonstrated that the higher incidence of nocturia among hyptertensive patients was more strongly associated (1.2 to 1.3 fold) among Black and Asian women, unrelated to their age or BMI status [624]. Another SR with moderate certainty of evidence based on the GRADE approach showed that nocturia was associated with a 1.2-fold increase risk of falls and possibly an approximately 1.3-fold increased risk of fractures [625]. Another SR and meta-analysis concluded that nocturia is probably associated with an ~1.3-fold increased risk of death [600].

The aetiology of nocturia is multifactorial and can include both urological and non-urological causes. Urological conditions which may exhibit nocturia as a significant symptom include OAB syndrome, BOO, DU and dysfunctional voiding. Non-urological causes include 24-hour polyuria (which includes nocturnal polyuria), congestive heart failure, sleep apnoea, restless leg syndrome, peripheral vascular disease, sleep disorders, night-time food ingestion, dependent oedema, and excessive fluid intake [626]. Given the varied aetiology of this symptom, there are a range of possible pathophysiological mechanisms, including: (1) 24-hour polyuria (e.g., diabetes mellitus, primary polydipsia, and diabetes insipidus); (2) nocturnal polyuria (e.g., behavioural, peripheral oedema, obstructive sleep apnoea, glycosuria, hormonal abnormalities and cardiac dysfunction); (3) diminished bladder capacity (e.g., OAB syndrome/detrusor overactivity, PFM dysfunction, BOO, pharmaceuticals, LUT calculi or tumours, and neurological bladder dysfunction); and (4) primary or secondary sleep disorders [627].

In postmenopausal women the relative deficiency in endogenous estrogen production is thought to exacerbate all major pathophysiological mechanisms that may underlie nocturia [628].

*4.6.2 **Classification***

Classification of nocturia is dependent on bladder diary analysis and several parameters have been defined as important [629]:

- nocturnal urine volume – total volume of urine passed during the night (this includes the first morning void but does not include the last void prior to sleep);
- maximum voided volume – largest single voided volume in 24 hours;
- nocturia index – nocturnal urine volume divided by maximum voided volume;
- nocturnal polyuria index – nocturnal urine volume divided by 24-hour urine volume;
- nocturnal urine production – nocturnal urine volume divided by duration of sleep in hours.

Analysis of these parameters allows clinical classification of nocturia based on physiological abnormalities that can cause nocturia:

- 24-hour polyuria;
- nocturnal polyuria;
- diminished bladder capacity;
- sleep disorders.

*4.6.3 **Diagnostic evaluation***

Evaluation of nocturia should include a thorough medical history and physical examination with particular reference to history of sleep disorders, fluid balance, associated LUTS, cardiovascular and endocrine comorbidity, renal disease, current medications and history of urological disease [629]. There are several nocturia-specific symptom scores, such as the ICI Questionnaire-Nocturia, Nocturia Quality of Life Questionnaire (N-QoL) and Nocturia Impact Diary; some of which were developed in men. A further screening

tool that aims to identify causes of nocturia is the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO) assessment tool [630-632].

A bladder diary is a vital initial investigation tool in patients complaining of nocturia and further supplementary investigations are guided by any abnormalities identified. Bladder diary analysis can allow for calculation of the parameters detailed in Section 4.6.2. A low nocturnal bladder capacity or global bladder capacity will be highlighted by reduced voided volumes during nocturnal hours or both night and day. This suggests an underlying urological condition such as OAB syndrome, BOO or DU. The term 24-hour polyuria is defined as 24-hour urine production > 40 mL/kg [633] and may be present in conditions such as diabetes mellitus or diabetes insipidus. The definition of nocturnal polyuria is age dependent and the thresholds for this diagnosis range from 20% (in younger persons) to 33% (age > 65 years) of the 24-hour urine volume produced during sleep. This may also be observed in patients with loss of circadian rhythm, cardiovascular disease, sleep apnoea, or sleep disorders [629]. A large study conducted across European and American centres involving ~2000 patients identified nocturnal polyuria as a contributory cause of nocturia in 89% of patients who were being treated for LUT abnormalities such as OAB syndrome or benign prostatic enlargement [634].

As an alternative to the ≥ 3-day bladder diary a nocturnal-only diary has been investigated in men [635]. The results showed acceptable sensitivity and specificity for the nocturnal bladder diary compared with the standard bladder diary for most parameters. The nocturnal-only diary was not able to diagnose 24-hour polyuria and has not yet been validated for use in women.

4.6.3.1 Summary of evidence and recommendations for diagnosis of nocturia

Summary of evidence	**LE**
A thorough medical history is an integral part of the evaluation of women presenting with nocturia.	4
Nocturia-specific questionnaires are sensitive to symptom changes.	3
A bladder diary allows for calculation of important indices and can identify potential causes of nocturia.	3
Nocturnal-only bladder diaries have been evaluated in men only.	3

Recommendations	**Strength rating**
Take a complete medical history from women with nocturia.	Strong
Use a validated questionnaire during assessment of women with nocturia and for re-evaluation during and/or after treatment.	Weak
Use a three-day bladder diary to assess nocturia in women.	Strong
Do not use nocturnal-only bladder diaries to evaluate nocturia in women.	Weak

*4.6.4 **Disease management***

When evaluating the results of trials involving treatment strategies for nocturia, it is vital to examine for clinical significance as statistical significance can be achieved with small reductions in nocturia episodes.

4.6.4.1 Conservative management

The individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. Interventions such as those listed below may help with nocturia but, for the majority, no quantification of their effect is possible:

- reduction of fluid intake at specific times;
- avoidance/moderation of intake of caffeine or alcohol;
- distraction techniques;
- bladder retraining;
- pelvic floor muscle training;
- reviewing medication;
- treatment of constipation.

The available data for conservative treatment of nocturia show significant heterogeneity. In the EAU SR [636], three studies [637-639] were favourable for conservative treatment with PFMT, with another failing to confirm a benefit [640].

The highest level of evidence comes from a study of 131 patients (a secondary analysis from a prospective RCT that had urgency-predominant UI as the primary inclusion criterion). The study found that training in PFM

contraction, which included four sessions of biofeedback-assisted PFMT reduced nocturia by a median 0.50 episodes per night and was significantly more effective than anticholinergic drug treatment or placebo [637]. The certainty of evidence associated with this treatment is moderate.

A smaller RCT of 50 women with urinary complaints, randomised 1:1 to bladder training and PFMT compared with a control group receiving no treatment, showed a significant decrease in patients' complaints of nocturia [638]. Another RCT in only 24 women compared PFMT only to transcutaneous electrical nerve stimulation therapy plus PFMT [639]. Although the authors did not find significant differences between the groups, the change in nocturia episodes before and after treatment was statistically significant in both groups. This study [641] was underpowered by the authors' own admission. The level of certainty of the evidence from these two trials is low. A large randomised, two-arm, parallel design, superiority trial (n = 647; women), compared the effects of unsupervised behavioural PFMT programs delivered in a two-hour class format and 20 minutes video format on UI prevention. No significant between-group differences of nocturia were observed at three months and twelve months, but at 24 months, women in the two hour class group were less likely to have fewer nocturia episodes (OR: 0.5; 95% CI: 0.3-0.7; p = 0.005) compared with those in the 20 minutes video group, but the authors concluded that the evidence is not sufficient to support one management strategy [642].

A multicentre, open-labeled, RCT evaluated whether cognitive behavioural therapy (CBT) using a self-assesment via a checklist is effective in improving nocturia in a mixed population (30/78 women). The mean rate of achievement of the CBT group was 64.4%. There was no significant difference between the two groups in night-time frequency based on the IPSS Q7 at four weeks but episodes of nocturia on the frequency volume chart (FVC) were significantly smaller in the CBT group (1.9 ± 0.9) than in the control group (2.4 ± 1.3; p = 0.039) [643].

In a secondary analysis from a prospective RCT, 210 women with UUI were evaluated for change from baseline in the number of episodes of nocturia and nocturnal incontinence between groups allocated to medical treatment (tolterodine ER 4 mg) alone vs. medical treatment plus PFMT [640]. No significant difference between the groups was found and the actual difference in nocturia episodes in either treatment arm was small. The level of certainty of the evidence from this trial is low.

A recent RCT has explored both individual and group PFMT with a specific secondary outcome of number of patients with two or more nocturia episodes per night [344]. The authors reported similar reductions, with > 30% of patients who had ≥ 2 episodes of nocturia at baseline no longer experiencing this level of symptoms at one year after PFMT.

One small, single-centre RCT in which functional magnetic stimulation was compared with no treatment in 39 women reported a significant decrease in nocturia (together with voiding frequency and pad use) in the treatment group compared with the control group [644].

In patients with obstructive sleep apnoea who complain of nocturia, continuous positive airway pressure has been shown to be effective in a SR and meta-analysis of five RCTs involving both sexes [645]. This treatment was associated with an average numerical reduction in nocturia of > 2 episodes per night.

4.6.4.1.1 Summary of evidence and recommendations for the conservative management of nocturia

Summary of evidence	**LE**
Individual or group PFMT appears to be equally effective for reduction in nocturia episodes.	1b
Most studies evaluating PFMT for nocturia in women with additional urinary symptoms have shown positive results compared with placebo or anticholinergic drugs.	1b
Treatment of nocturia secondary to obstructive sleep apnoea with continuous positive airway pressure reduces nocturia episodes.	1a

Recommendations	**Strength rating**
Offer women with lower urinary tract symptoms (LUTS) lifestyle advice prior to, or concurrent with, treatment.	Strong
Offer pelvic floor muscle training for nocturia (either individually or in the group setting) to women with urinary incontinence or other storage LUTS.	Strong
Offer women with nocturia and a history suggestive of obstructive sleep apnoea a referral to a sleep clinic for assessment of suitability for continuous positive airway pressure treatment.	Strong

4.6.4.2 Pharmacological management

4.6.4.2.1 Desmopressin

Desmopressin is a synthetic analogue of the hormone vasopressin and is most often used for management of nocturia due to nocturnal polyuria. In a recent SR [636], three trials specifically conducted in women were found but more additional data could be extracted from studies in mixed populations. The earliest evidence comes from a 1982 single-site crossover trial involving 25 women treated with 20 µg desmopressin or placebo and revealed a significant decrease in nocturnal urine output at six weeks [646]. A more recent multicentre, multinational double-blind RCT involving 141 women used desmopressin 0.1, 0.2 or 0.4 mg orally at bedtime after a dose-titration period [647]. This increased the likelihood of a positive outcome because non-responders were excluded at that stage. At three weeks, significant reductions in nocturnal urinary frequency and nocturnal diuresis were reported. In another multicentre double-blind RCT, 58 women were randomised into five groups (twelve receiving placebo, twelve desmopressin 10 µg, eleven desmopressin 25 µg, eleven desmopressin 50 µg and twelve desmopressin 100 µg) for four weeks [648]. A dose–response relationship was observed and women appeared more sensitive than men to desmopressin. Significant changes in nocturnal urine volumes were reported in favour of the higher desmopressin doses. Differences in the nocturnal polyuria index also tended to favour desmopressin over placebo and the higher desmopressin doses. The level of certainty of the evidence from these trials is low.

Desmopressin can be safely combined with anticholinergics with significant benefit in women with OAB and nocturnal polyuria, as shown by a multicentre RCT of 97 patients [649]. A *post hoc* analysis of data comparing three-month once-daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57) revealed a significant reduction in nocturnal void volume and time to first nocturnal void in favour of combination therapy. The level of certainty of the evidence from this trial is moderate.

Pooled data from three RCTs were used to examine the adverse event profile of desmopressin, specifically hyponatraemia [650]. The authors reported that the majority tolerate desmopressin treatment without clinically significant hyponatraemia, but risk increased with age and lower baseline serum sodium concentration. They advised that desmopressin treatment in elderly patients should include careful monitoring of the serum sodium concentration and should be avoided in patients with a baseline serum sodium concentration below normal range [650].

4.6.4.2.2 Anticholinergics

A SR [636] identified three RCTs involving anticholinergics such as oxybutynin 2.5 mg/day [637] and tolterodine 4 mg/day [640, 649]. A secondary analysis from a prospective RCT involving 131 women with nocturia followed up for eight weeks found that women receiving 2.5 mg immediate-release oxybutynin once daily (with the possibility of self-titration and dose escalation to 5 mg three times daily) had fewer nocturia episodes than women receiving placebo [637]. Women receiving oxybutynin plus behavioural therapy also exhibited a significant decrease in nocturia episodes compared with placebo and oxybutynin alone. A multicentre RCT with 305 women followed up for eight weeks examined the efficacy of tolterodine tartrate 4 mg alone or in combination with behavioural training [640]. Significant differences compared with baseline were observed in mean nocturia episodes and nocturnal incontinence episodes in both groups, but no difference was reported between the two treatment groups. The level of certainty of the evidence from this trial is moderate.

In an RCT including 97 women with nocturnal polyuria and OAB syndrome, comparing three months of once daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57), a significant reduction in mean number of nocturnal voids compared with baseline was reported in both groups [649]. The level of certainty of the evidence from this trial is moderate.

A large comparative study followed 407 women with OAB and nocturia for four weeks [651]. The patients were given tolterodine as monotherapy in one group, and tolterodine combined with estazolam (a benzodiazepine) in the other group. Significant changes from baseline in both groups for the main outcome of number of nocturia episodes were reported. Combination therapy showed a significant benefit for women with OAB and nocturia compared with monotherapy in terms of differences in number of nocturia episodes, urgency episodes in 24 hours, UUI episodes in 24 hours, and voided volume per micturition. The level of certainty of the evidence from this trial is very low.

A small multicentre RCT compared oxybutynin patch vs. mirabegron on nocturia-related QoL in women with OAB. Both treatments showed improvements in N-QoL score at four weeks, but mirabegron showed statistical differences at eight weeks. Additionally, only mirabegron decreased nocturnal frequency and water intake, and prolonged hours of uninterrupted sleep eight weeks after administration with statistical significance, whereas oxybutynin patch did not [652].

4.6.4.2.3 Oestrogens

In a recent SR [636] only a single RCT investigating the efficacy of oestrogen for nocturia was identified [653]. This trial compared an oestradiol-releasing vaginal ring with an oestriol vaginal pessary in 251 women followed up for six months. There was no difference between the treatment groups in the number of women reporting nocturia, although they reported significant change from baseline in both treatment arms with > 50% of subjects responding in each arm. The certainty of evidence for this outcome was low.

4.6.4.2.4 Diuretic treatment

In a randomised placebo-controlled study an afternoon dose of 40 mg furosemide (taken six hours before bedtime) in an attempt to establish complete diuresis before bedtime was given to elderly men [654]. In the 43 men who completed the study, night-time frequency in the furosemide group fell by 0.5 episodes compared with placebo, and percentage night-time voided volume fell by 18%. No such study has been carried out in female patients.

4.6.4.3 Summary of evidence and recommendations for pharmacological management of nocturia

Summary of evidence	**LE**
Desmopressin treatment for nocturia shows significant reductions in nocturnal urine output, nocturnal urinary frequency and nocturnal polyuria index.	1b
Most nocturia patients tolerate desmopressin treatment without clinically significant hyponatraemia; however, the risk increases with increasing age and decreasing baseline serum sodium concentration.	1a
Treatment of nocturia in OAB patients with anticholinergic drugs shows reduction in nocturia episodes.	1b
Combination of PFMT and pharmacological treatment with anticholinergics does not appear to confer additional benefit over anticholinergics alone.	1b
Combination of anticholinergic and desmopressin treatment appears to reduce nocturnal voided volume and time to first nocturnal void in women with nocturnal polyuria.	1b
Vaginal oestrogen may be beneficial in the treatment of nocturia in around 50% of women.	1b
Afternoon (timed) diuretic treatment with furosemide reduces nocturia episodes and nocturnal voided volume in men but no similar studies have been conducted in women.	1b
Examination for clinical significance is important when evaluating trials involving treatment strategies for nocturia, as statistical significance can be achieved with small reductions in nocturia episodes.	3

Recommendations	**Strength rating**
Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women, following appropriate counselling regarding the potential benefits and associated risks (including hyponatraemia).	Strong
Carefully monitor serum sodium concentration in elderly patients treated with desmopressin. Avoid prescribing desmopressin to patients with a baseline serum sodium concentration below normal range.	Strong
Offer anticholinergic treatment for nocturia to women with urgency urinary incontinence or other lower urinary tract symptoms, following appropriate counselling regarding the potential benefits and associated risks.	Strong
Inform women with nocturia that combination of behavioural therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone.	Weak
Offer combination of anticholinergics and desmopressin to women with overactive bladder and nocturia secondary to nocturnal polyuria, following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer vaginal oestrogen treatment to women with nocturia, following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer timed diuretic treatment to women with nocturia secondary to polyuria, following appropriate counselling regarding the potential benefits and associated risks.	Weak

4.6.4.4 Surgical management

Surgical treatment is generally reserved for those with underlying correctable LUT disorders. The effect of surgical treatments on symptoms of nocturia can be found in the relevant condition-specific sections of this guideline.

4.6.5 ***Follow-up***

Follow-up of patients with nocturia is dependent on the underlying aetiology of this symptom and the treatment given.

4.7 Pelvic organ prolapse and lower urinary tract symptoms

4.7.1 Epidemiology, aetiology, pathophysiology

Pelvic organ prolapse is a common condition in adult women. The prevalence of POP is 3–6% when bothersome symptoms are used to characterise the condition and increases to 50% when a purely anatomical definition is used [655].

The estimated lifetime risk for POP surgery is 12.6% [656]. Parity, vaginal delivery, ageing and obesity are the most commonly recognised risk factors [657].

Although the aetiology of POP is not fully understood, birth trauma to the levator ani complex is recognised as central to its development. In normal physiology, an intact levator ani complex functionally closes the genital hiatus surrounding the vagina, limiting the pressure gradient between the intra-abdominal and intravaginal areas. During physical activities, this reduces stress on the endopelvic fascia and its condensations (e.g., ligaments), which are crucial in securing the bladder, uterus and rectum to their surroundings. Current aetiological concepts include widening of the levator hiatus due to birth trauma, which creates a low-pressure area in the vagina and consequently increased stress on the ligaments, fascial elements and PFMs during physical activity. When the supporting function of the muscles and connective tissues fails, POP may develop [658]. This concept also explains the time lapse between birth trauma and occurrence of POP.

Pelvic organ prolapse and LUTS often occur simultaneously in women. In isolation, both POP and LUTS are prevalent conditions in women, although the prevalence of LUTS in women with POP exceeds that of LUTS in women without POP [655]. The observation that LUTS may improve or worsen after POP treatment suggests a link between these two entities [655]. Clinical examples include the occurrence of BOO symptoms in severe POP, and disappearance of SUI symptoms with progression of POP (and conversely the occurrence of SUI after treatment of POP) [659].

4.7.2 Classification

Since 1996, POP has been classified according to the Pelvic Organ Prolapse-Quantification (POP-Q) system [660]. For specifics on how to perform the POP-Q measurement and the nine standard points to be measured (Figures 2 and 3), we refer to the original publications [660, 661].

The vagina is divided into anterior (bladder), posterior (rectum) and apical (cervix or vaginal vault) compartments. After scoring the position of the nine POP-Q points, a prolapse of each compartment is graded numerically from stage 0 to 4, with stage 0 being no prolapse and stage 4 being complete eversion of the compartment. A crucial marker in staging POP is the hymenal remnant. Any POP with a maximum descent that is still 1 cm above the hymen (e.g., in the vagina) is considered a stage 1 POP. A maximum descent between 1 cm above and 1 cm below (outside the vagina) the hymen is a stage 2 POP. Any descent beyond 1 cm below the hymen is a stage 3 POP.

The figures below show the POP-Q staging in comparison to the Baden–Walker system (and others) used before the international consensus on the POP-Q staging was introduced as the new standard.

Figure 2: Prolapse classification system

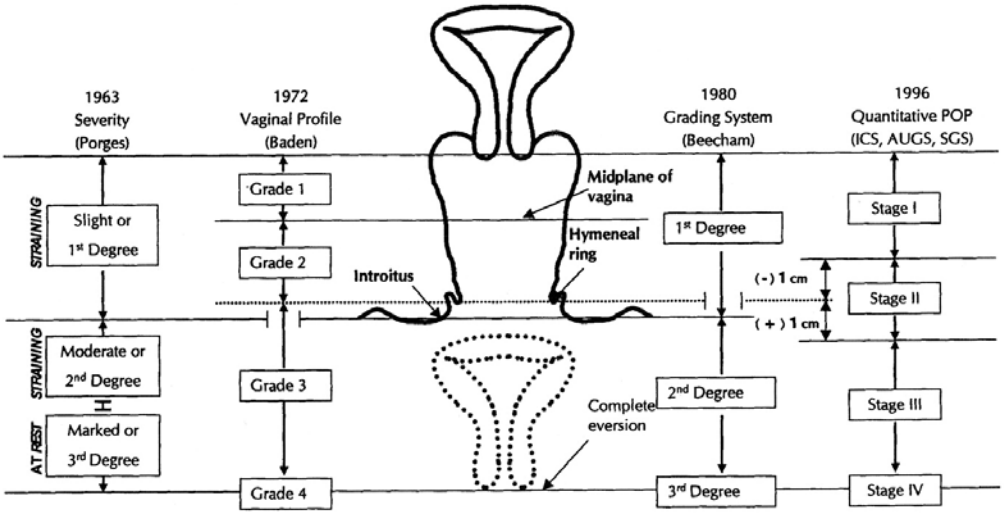


Figure reproduced with permission from the publisher, from Theofratus JP et al. [630].

Figure: 3: Pelvic Organ Prolapse-Quantification staging

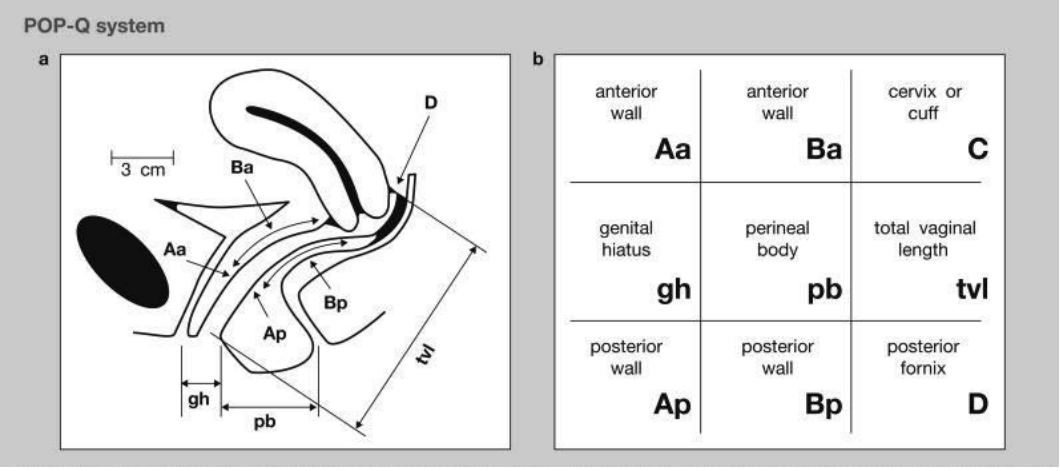


Figure reproduced with permission from the publisher, from Bump RC et al, [629]. The standardisation of terminology of female POP and pelvic floor dysfunction.

4.7.3 ***Diagnostic evaluation***

Pelvic organ prolapse is a clinical diagnosis and is staged according to the POP-Q system. Pelvic organ prolapse that is above the hymen should only produce mild symptoms at most [662]. In cases where there is a discrepancy between the clinical symptoms and POP-Q staging, it is advised to consider performing the POP-Q measurement in a standing rather than supine position, or re-evaluating at a later time in the day. Magnetic resonance imaging assessment demonstrated a marked difference in POP staging between supine and standing position [663]. Additional diagnostic tests for POP are mainly indicated if there are accompanying symptoms like LUTS or bowel dysfunction. Imaging techniques are not advised for the routine diagnostic work-up of patients presenting with POP [67]. The role of urodynamics in the diagnostic work-up of SUI has been discussed in the SUI, Section 4.2, of this guideline.

The use of techniques to reduce POP during urodynamic evaluation to diagnose occult SUI is common practice. This information may be used to decide if additional anti-UI surgery should be offered at the time of POP surgery or to counsel patients on the possible after-effects of POP treatment.

There are several POP reduction methods that may be used during physical examination or urodynamic evaluation. In a multicentre observational study, five different cough/stress tests were compared for their ability to detect SUI in women with POP [664]. Stress urinary incontinence during at least one of the five tests occurred in 60/205 (29.2%) women without SUI symptoms. Looking at single test performance, the detection rate of occult SUI in women without symptoms increased from 4.4% in case of no reduction to 22% in case of reduction with a pessary.

A large randomised trial included women with POP without symptoms of SUI, who were randomised to sacro-colpopexy with or without Burch colposuspension [665]. Three hundred and twenty-two stress-continent women with stages 2–4 prolapse underwent standardised urodynamic testing, and the protocol included five prolapse reduction methods. Preoperatively, twelve of 313 (3.7%) women demonstrated urodynamic SUI without prolapse reduction. Preoperative detection of urodynamic SUI with prolapse reduction at 300 mL was by pessary, 6% (5/88); manual, 16% (19/122); forceps, 21% (21/98); swab, 20% (32/158); and speculum, 30% (35/118). Another large trial included women with POP without SUI symptoms randomised to vaginal POP surgery with or without (sham incision) MUS [666]. Before surgery, 33.5% (111/331) of women demonstrated SUI at a prolapse-reduction cough stress test. In an observational study of 172 women with POP without SUI, 19% of women were diagnosed with occult SUI by basic office evaluation (with prolapse reduction with swab on forceps) and 29% on urodynamic evaluation [667].

In summary, SUI can be demonstrated in women with POP without symptoms of SUI after POP reduction in up to 30% of cases. There is no consensus on the best reduction technique.

Although the detection rate of occult SUI increases after reduction of POP in women without SUI symptoms, its clinical value is under debate.

In one trial, preoperative stress-continent women were evaluated during urodynamic testing with prolapse reduction to determine if they were more likely to report postoperative SUI, regardless of concomitant colposuspension (controls 58% vs. 38% and Burch colposuspension 32% vs. 21%) [665]. In another trial, women with SUI during the cough stress test after POP reduction reported UI at three months in 29.6% in the synthetic MUS group, compared with 71.9% in the sham group [666]. Women with a positive prolapse reduction stress test before surgery appeared to receive more benefit from a synthetic MUS at three months, but not at twelve months, than did those with a negative test.

In a large observational study, women did not receive additional anti-UI surgery even if they had SUI after POP reduction preoperatively. In this scenario, 9% (16/172) of women developed postoperative *de novo* SUI and six underwent surgery for *de novo* SUI [667]. Women with demonstrable preoperative SUI were more at risk of postoperative SUI: 28% vs. 5%. Based on urodynamic evaluation only, one more woman was predicted to have postoperative SUI, but all six women who underwent treatment for *de novo* SUI showed SUI during basic office evaluation.

In a model developed to predict the risk of *de novo* SUI in women undergoing POP surgery based on findings from two trials, twelve preoperative predictors were tested [668]. Positive SUI during a preoperative prolapse reduction test was included in this model, but it failed to be a significant predictor as a single item. Preoperative POP stage was not associated with risk of *de novo* SUI.

4.7.3.1 Summary of evidence and recommendation for detection of SUI in women with POP

Summary of evidence	**LE**
Pelvic organ prolapse reduction during cough stress test, in office or during urodynamics detects SUI in ~30% of continent women.	2a
Women with SUI after POP reduction preoperatively (occult SUI) are likely to be at increased risk of developing SUI symptoms after POP surgery.	2a

Recommendation	**Strength rating**
Perform pelvic organ prolapse (POP) reduction test in continent women to identify those with occult stress urinary incontinence and counsel them about the pros and cons of additional anti-incontinence surgery at the time of POP surgery.	Strong

4.7.3.2 Urodynamics in women with pelvic organ prolapse and LUTS (without stress urinary incontinence)

The role of urodynamics is less clear in women presenting with POP and concurrent LUTS, other than SUI. Pelvic organ prolapse is a complex condition incorporating different compartments of the vagina, and presenting at different stages of severity. Information about detrusor activity, as assessed with urodynamics, may provide information about the risk of developing DO after surgery, but also on the risk of urinary retention due to DU. An observational study assessed predictors for DO following POP surgery for POP-Q stage three or higher in 1503 women and the authors concluded that preoperative maximum urethral closure pressure ≥ 60 cm H_2O, Qmax < 15 mL/s, maximum detrusor voiding pressure (Dmax) > 20 cm H_2O and PVR volume > 200 mL were independent risk factors for postoperative DO [669]. A small observational study (n = 49) evaluated patients with preoperative DU (detrusor pressure at maximum flow was ≤ 10 cm H_2O and Q_{max} ≤ 12 mL/s) after POP surgery. Surgery objectively cured DU in 47% of women and urodynamic findings normalised after surgery [670]. The 2019 NICE guidelines do not include a recommendation to perform urodynamics as part of the diagnostic work-up of POP, except for combination with symptomatic SUI [67].

*4.7.4 **Disease management***

Pelvic organ prolapse symptoms can be treated with PFMT, vaginal pessary, surgery or a combination of these treatments. The scope of these guidelines is to focus on LUTS in women; therefore, only data on the effect of treatment of urinary symptoms are presented.

4.7.4.1 Conservative management of pelvic organ prolapse

The 2013 NICE guideline on Urinary Incontinence and POP in Women had an updated management section in 2019, including a full evidence review [67]. The overall conclusion with respect to conservative treatment for POP was that the evidence is of low quality. Thirteen RCTs were identified. Seven studies presented data on changes in urinary symptoms [671-677]. An additional search identified four RCTs that addressed the addition

of PFMT to POP surgery [678-681], and one that compared combined PFMT/Pilates therapy with lifestyle advice by leaflet [682].

Five studies [672, 674-676, 682] compared PFMT to lifestyle advice/leaflet; one study [673] compared PFMT alone to PFMT with pessary; one study [677] compared PFMT to pessary therapy; and five studies compared surgery for POP with or without addition of PFMT [671, 678-681].

4.7.4.1.1 Pelvic floor muscle training versus lifestyle advice

An RCT (n = 109) reported that, at six months' follow-up, the ICIQ-UI-SF scores improved in favour of the PFMT group compared with a control group receiving lifestyle advice only (difference from baseline PFMT 2.40 points and control 0.2 points) [672]. However, the difference of 2.4 points from baseline, in favour of PFMT, has to be viewed with caution as the mean baseline score in the PFMT group was higher than in the control group (7.4 vs. 5.9). Likewise, it has to be noted that the absolute ICIQ-UI-SF values at six months' follow-up were not significantly different between PFMT (4.8) and controls (5.2).

Two publications from one RCT reported on the three-, six- and twelve-month results of lifestyle advice only vs. lifestyle advice combined with group PFMT [674, 675]. The Urogenital Distress Inventory-6 (UDI-6) and Urinary Impact Questionnaire-7 (UIQ-7) questionnaires were used to assess urinary symptoms. At three months' follow-up, both groups (53 women in the lifestyle group and 56 in the lifestyle + PFMT cohort) reported significantly improved UDI-6 scores, while the lifestyle-only group also reported significantly greater improvement in the UIQ-7 score. Between-group comparison showed no differences in UDI-6 and UIQ-7 scores at six months. At twelve months' follow-up, the majority of women had sought additional treatment (70% in the lifestyle-only group and 48% in the lifestyle/PFMT group). The number of patients remaining on the original therapy was too small to reach strong conclusions.

One RCT reported on six and twelve months' follow-up of 225 women with POP-Q stage 1–3 randomised to individualised PFMT and 222 women randomised to lifestyle leaflet information only (control) [676]. Urinary symptoms were assessed with a single question on the existence of UI; a single question regarding the need to strain to void; and a single question regarding incomplete bladder emptying; these were supplemented with the ICIQ-SF questionnaire score. At six months, significantly more women in the control group reported UI, the need to strain to empty their bladder, and the feeling of incomplete emptying compared to the PFMT group. The score on the ICIQ-SF was also significantly worse in the control group as compared to the PFMT group. However, at twelve months, there was no significant difference in these items between groups. It has to be noted that 50% in the control group received additional treatment within the twelve-month study period. Twenty-seven percent had additional PFMT, which may have had an effect on the twelve-month data.

Another RCT reported on the 24-month follow-up of 414 women with stage 1–3 POP (207 assigned to PFMT/Pilates and 207 to lifestyle advice) [682]. Urinary symptoms were assessed with the ICIQ-UI-SF and a question about UI and difficulty emptying the bladder. At 24 months, the ICIQ-UI-SF score was significantly better in the intervention group (mean difference –0.83). However, the proportion of women reporting any UI did not differ between the groups, nor did the number of pads used weekly.

4.7.4.1.2 Pelvic floor muscle training versus pelvic floor muscle training with pessary

One RCT compared PFMT alone to PFMT and pessary for symptomatic POP [673]. Urinary tract symptom changes were assessed using UDI-6 and UIQ at six and twelve month's follow-up. At twelve months, there was no difference in the between-group comparison. With respect to the UIQ, women in the pessary/PFMT group showed a significant improvement from baseline, but the PFMT-only group did not. Women in the pessary/PFMT group reported significantly more frequent *de novo* SUI (48% vs. 22%), and more improvement of pre-existing voiding difficulty (62.5% vs. 35.5%).

4.7.4.1.3 Pelvic floor muscle training versus pessary only

One RCT reported on the 24-month follow-up of 82 women with symptomatic POP randomised to pessary therapy and 80 women randomised to PFMT [683]. The UDI-6 was used as the outcome measure for urinary symptoms. Both in the ITT and per protocol analyses, the UDI score did not differ significantly between groups at 24 months of follow-up.

4.7.4.1.4 Surgery alone versus surgery with pelvic floor muscle training

An assessor-blinded RCT compared surgery for POP with or without additional pre-and postoperative PFMT. At twelve months after surgery, there were no significant differences between the groups on the change in scores of the UDI nor the IIQ scores [671].

Another RCT reported on the six-month follow-up of 57 women (28 surgery/29 surgery with PFMT). The UDI-6 was used to assess urinary symptoms. There was a significant improvement in the UDI-6 score for both groups, but not between groups [679].

Another RCT reported on the results of a 2x2 factorial design in which women were first randomised between two surgical techniques for POP and between additional PFMT (n = 188) or not (n = 186) [680]. The UDI was used to assess urinary symptoms up to 24 months. No significant differences were found between the addition of PFMT to surgery or not. Another study of the same population reported on SUI in particular [681]. No significant differences were found between women who had additional PFMT and those who had not.

In 2020 an RCT reported on 40 and 90 days' follow-up of 48 women randomised to supervised PFMT before and after surgery and 40 women having surgery only [678]. UDI-6 was used to assess urinary symptoms. No significant differences in UDI-6 scores were identified at 40 and 90 days.

The NICE guidelines on the management of POP advocate considering supervised PFMT for ≥ 16 weeks as initial treatment for symptomatic prolapse [67]. The use of pessary is also to be considered, alone or combined with PFMT. It is important to recognise that a benefit is expected on typical POP symptoms, like feeling or seeing a bulge out of the vagina, and not on LUTS, as the reported RCTs showed. From a urological perspective, initiating conservative treatment for asymptomatic POP in order to treat UI or bladder emptying problems is not supported by the data.

4.7.4.1.5 Pessary versus surgery alone

A prospective cohort study showed that surgery in comparison with pessary treatment resulted in statistically significant more women reporting subjective improvement [684].

4.7.4.1.6 Summary of evidence and recommendation for the conservative treatment of pelvic organ prolapse and lower urinary tract symptoms

Summary of evidence	**LE**
Pelvic floor muscle therapy improves LUTS for up to six months in POP patients who do not have additional pessary or surgical treatment.	2a
If pessary therapy or surgical intervention is used for POP, PFMT does not show an additional benefit.	2a

Recommendations	**Strength rating**
Inform women with pelvic organ prolapse (POP), who do not need a vaginal pessary or surgical intervention, about the potential relief from lower urinary tract symptoms (LUTS) from pelvic floor muscle therapy (PFMT).	Strong
Do not offer preoperative PFMT to improve outcome of LUTS if pessary therapy or surgical intervention is indicated for POP.	Strong

4.7.4.2 Pelvic organ prolapse surgery and overactive bladder

Only a few studies have specifically addressed the effect of POP surgery on OAB symptoms. A SR of twelve studies, excluding women with SUI, evaluated OAB symptoms before and after surgery [685]. All but one study reported improvement of OAB symptoms. The same authors performed a prospective analysis of 505 women who had POP surgery with or without mesh [686]. Symptoms were assessed with UDI questions and each symptom was dichotomised into not bothersome or bothersome. Mean follow-up was 12.7 months. The incidence of bothersome urinary frequency reduced from 36.6% to 14.6%, with *de novo* symptoms occurring in 6.1% of women. Bothersome urgency symptoms reduced in 36.8% to 12.9% of women, with 5.0% developing *de novo* symptoms. Urgency urinary incontinence symptoms reduced from 21.2% to 6.1% of women, with 5.3% developing *de novo* symptoms.

One observational study evaluated frequency and urgency symptoms without consideration of bother in 87 women undergoing POP surgery and showed an improvement in frequency by 75%, and in urgency in 83% [687]. The effect of the POP-Q stage did not seem to influence the effect of surgery on OAB symptoms [686, 687].

Another observational study (n = 43) evaluated the effect of posterior repair on OAB/DO and showed a 70–75% improvement rate in both parameters after surgery [688].

4.7.4.3 Pelvic organ prolapse surgery and bladder outlet obstruction

The criteria for BOO are based on urodynamic assessment. Pelvic organ prolapse can be categorised as anatomical BOO, which is addressed in Sections 4.5.2.2 and 4.5.3.1.

4.7.4.4 Pelvic organ prolapse surgery and stress urinary incontinence

The aim of this section is to address the options available to women who require surgery for POP and who have associated SUI (either before or after reduction of prolapse), and to assess the value of prophylactic anti-UI surgery in women with no evidence of SUI.

A SR and meta-analysis of ten trials on prolapse surgery with or without an anti-incontinence procedure was reported in 2018 [689]. In addition, a Cochrane review including nineteen trials (n = 2,717) evaluating bladder function after surgery for POP presented analyses of women with POP and SUI, women with POP and occult SUI, and women with POP who were continent [690].

4.7.4.4.1 Vaginal pelvic organ prolapse surgery in women with stress urinary incontinence

Two trials addressed postoperative SUI in patients who had been diagnosed with SUI preoperatively and had vaginal POP surgery [691, 692]. Two trials (n = 185 and 134) compared the use of MUS at initial POP surgery to POP surgery alone. The RR for postoperative SUI was 0.30 in favour of the combined POP surgery and MUS group. One of these two trials also compared the use of MUS at initial POP surgery and at three months if SUI persisted [691]. At twelve months' follow-up, there was no difference between the groups regarding postoperative UI (RR 0.41); however, 44% of the women without initial MUS never required surgery and 29% were dry.

4.7.4.4.2 Abdominal pelvic organ prolapse surgery in women with stress urinary incontinence

One RCT randomised 47 women with POP and SUI to an abdominal POP surgical procedure; e.g., sacro-colpopexy with or without Burch colposuspension. Additional SUI surgery did not improve postoperative SUI as compared to sacro-colpopexy alone (RR: 1.38) [693]. This finding remained consistent over five years' follow-up [694]. Another RCT compared the addition of a MUS or Burch colposuspension to an abdominal sacro-colpopexy in 113 women with POP and SUI [695]. At two years' follow-up, the RR for postoperative SUI was 0.54 in favour of the MUS group.

4.7.4.5 Vaginal pelvic organ prolapse surgery in continent women

One RCT compared vaginal POP surgery alone with concomitant POP surgery and MUS in 220 women. Postoperative SUI occurred in 46/113 (40.7%) women who had POP surgery alone, compared to 30/107 (28.0%) who had additional MUS (RR: 0.69) [690].

4.7.4.5.1 Abdominal pelvic organ prolapse surgery in continent women

Two RCTs compared abdominal sacro-colpopexy with (n = 189) or without (n = 190) Burch colposuspension with an outcome favouring the addition of Burch colposuspension (RR for *de novo* SUI: 0.69) [696, 697].

4.7.4.5.2 Vaginal pelvic organ prolapse surgery in women with prolapse and occult stress urinary incontinence

Five RCTs including a total of 194 women who had vaginal POP repair alone and 174 women who had an additional MUS at the time of primary surgery were identified [666, 698-701]. The RR of postoperative SUI was 0.38 in favour of the MUS group.

4.7.4.6 Adverse events associated with combined pelvic organ prolapse and stress urinary incontinence surgery

Data from six RCTs on vaginal POP surgery with MUS were pooled to assess adverse events [666, 691, 692, 699-701]. Urgency urinary incontinence was less frequent after combination surgery as compared to POP surgery alone (28% vs. 42%; RR: 0.7), but there was a tendency towards more voiding problems. Adverse events directly related to surgery occurred more often in the combination group (28% vs. 15%; RR: 1.8), as did serious adverse events such as bladder perforation, urethral injuries, and tape exposure (14% vs. 8%; RR 1.7) [689].

In summary, it is difficult to generalise the results of trials using different procedures to treat both POP and UI. It seems that with a combined procedure, the rate of postoperative SUI is lower but voiding symptoms and complication rates are higher. Studies using MUS have shown more significant differences in UI outcomes with combined procedures than when other types of anti-UI procedure have been used. It must be taken into account that although more women are dry after combined surgery for POP with MUS, there are potential adverse events that should be balanced against potential benefits.

4.7.5 *Summary of evidence and recommendations for surgery in women with both pelvic organ prolapse and stress urinary incontinence*

Summary of evidence	LE
Women with POP and UI	
Surgery for POP and SUI shows a higher rate of cure of UI in the short-term than POP surgery alone.	1a
There is conflicting evidence on the relative long-term benefit of surgery for POP and SUI vs. POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1a
Continent women with POP	
Continent women with POP are at risk of developing SUI postoperatively.	1a
The addition of a prophylactic anti-UI procedure reduces the risk of postoperative UI but increases the risk of adverse events.	1a
Women with POP and OAB	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of OAB.	2b

Recommendations for women requiring surgery for bothersome pelvic organ prolapse (POP) who have symptomatic or occult stress urinary incontinence (SUI)	**Strength rating**
Offer simultaneous surgery for POP and SUI only after a full discussion of the potential risks and benefits of combined surgery vs. POP surgery alone.	Strong
Inform women of the increased risk of adverse events with combined prolapse and anti-urinary incontinence surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome POP who do not have symptomatic or occult SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Warn women that the benefit of combined surgery for POP and SUI may be outweighed by the increased risk of adverse events compared to prolapse surgery alone.	Strong

4.8 Urinary fistula

The evidence relating to diagnosis and treatment of urinary fistulae is generally low level and largely composed of case series and other consensus statements. In particular, the epidemiology, aetiology, diagnosis, treatment and prevention of obstetric and non-obstetric fistulae have been described in detail during the 2016 ICI conference [702]. Most non-obstetric fistulae are iatrogenic in origin, with most caused by pelvic surgery (e.g., hysterectomy for benign or malignant conditions, bowel resection, and urological surgery). The risks during pelvic surgery increase relative to the complexity of the resection, the extent of primary disease, and prior radiotherapy (especially for recurrent disease). When a fistula occurs following radiotherapy for primary treatment, this may be an indication of tumour recurrence.

4.8.1 *Epidemiology, aetiology and pathophysiology*

4.8.1.1 *Obstetric fistula*

According to the WHO, fistulae affect > 2 million women, mostly from sub-Saharan African and Asian countries. The pooled prevalence of fistula from population studies is 0.29/1000 pregnancies [703]. Poor quality obstetric care, staff unaccountability, late referral, and poor nursing standards have been identified as health system causes [703]. However, obstructed labour is poorly documented. The main individual risk factors include age at first marriage, short stature, pregnancy with a male child, failure to attend antenatal care, low socio-economic status, low social class, lack of employment, and illiteracy [704-706]. Obstetric fistulae have detrimental consequences on global and individual health and are associated with malnutrition, sexual dysfunction, anxiety, depression, insomnia, social isolation, worsening poverty, and suicide [707, 708].

4.8.1.2 *Iatrogenic fistula*

Poor obstetric care is usually responsible for VVF in the developing world. By contrast, in the developed world, gynaecological or pelvic surgery is the main cause of VVF.

4.8.1.2.1 Post-gynaecological surgery

An injury to the urinary tract during hysterectomy for benign conditions (60–75%), hysterectomy for malignant conditions (30%) and caesarean section (6%) are the main causes of postoperative VVF in the developed world [709, 710]. The risk of pelvic organ fistula following hysterectomy ranges from 0.1 to 4% [711].

Fistulae may also occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, and/or chemotherapy.

In a study including 536 women undergoing radical hysterectomy for invasive cervical cancer, bladder injury occurred in 1.5% with VVFs forming in 2.6% and uretero-vaginal fistulae (UVFs) in 2.4% of cases [712]. Overall, the rate of urogenital fistula appears to be ~9 times higher following radical hysterectomy for malignant disease as compared to that following simple hysterectomy (abdominal or vaginal for benign conditions) [713]. Bladder-sparing techniques during pelvic exenteration can increase the risk of fistula formation [714].

4.8.1.2.2 Radiation fistula

The risk of fistula seems to be higher for postoperative external radiation (1.9%) compared to intravaginal brachytherapy (0.8%) [715], without any predictive factor being identified [716]. This is most likely due to the heterogeneity of data regarding the tumour type and stage, the form of radiation, and the site and dose delivered.

4.8.1.2.3 Rare causes of vesico-vaginal fistula

Foreign bodies such as pessaries, sex toys, cups etc. can be a cause of delayed presentation of VVF [717-719]. Ketamine abuse has also been shown to be responsible for fistula formation [720].

4.8.1.3 Summary of evidence for epidemiology, aetiology and pathophysiology of urinary fistula

Summary of evidence	**LE**
The risk of injury to the urinary tract and subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures.	2
The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment.	4

*4.8.2 **Classification***

Due to the plethora of VVF classification systems, a consensual classification system needs to be adopted. The Waaldijk and Goh classifications are widely used for diagnosis and follow-up [721-723]. They were originally designed for obstetric fistulae and their use in iatrogenic fistulae is less relevant [724]. Waaldijk's classification is based on the size and site of the fistulae and divides them into three main categories: type 1 are VVFs with no urethral involvement; type 2 are those that involve the urethra (and are sub-classified into those with circumferential and non-circumferential urethral involvement); and type 3 are fistulae involving other parts of the urinary tract. Goh's classification also uses the presence or absence of urethral involvement to sub-categorise VVFs and takes into account the degrees of fibrosis present. The WHO classification (Table 6) was originally developed for obstetric fistulae and separates fistulae into simple and complex.

Table 6: Adapted WHO Classification of fistulae [703]*****

Simple fistula with good prognosis	**Complex fistula with uncertain prognosis**
• Single fistula < 4 cm	• Fistula > 4 cm
• Vesico-vaginal fistula	• Multiple fistula
• Closing mechanism not involved	• Recto-vaginal mixed fistula, cervical fistula
• No circumferential defect	• Closing mechanism involved
• Minimal tissue loss	• Scarring
• Ureters not involved	• Circumferential defect
• First attempt to repair	• Extensive tissue loss
	• Intravaginal ureters
	• Failed previous repair
	• Radiation fistula

**Although this classification was developed for obstetric fistula initially, it could be relevant for iatrogenic fistula as well.*

4.8.2.1 Recommendation for the classification of urinary fistula

Recommendation	Strength rating
Use a classification system for urinary tract fistulae to try to standardise terminology in this subject area.	Strong

*4.8.3 **Diagnostic evaluation***

Leakage of urine is the hallmark sign of a urogenital fistula. The leakage is usually painless, may be intermittent if it is position dependent, but more usually is constant. Unfortunately, intraoperative diagnosis of a genito-urinary or gastrointestinal injury is made in only about half of cases [725]. Diagnosis of VVF usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection, cystoscopy, retrograde bladder filling with a coloured fluid, or placement of a tampon into the vagina to identify staining may facilitate diagnosis of VVF. A double-dye test to differentiate between UVF and VVF may be useful in some cases [710]. Testing the creatinine level in either the extravasated or collected fluid will confirm fluid leakage as urine. Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the possible presence of associated urinoma. Magnetic resonance imaging, in particular with T2 weighting, also provides diagnostic information regarding fistulae [726].

*4.8.4 **Disease management of fistula***

4.8.4.1 Management of vesico-vaginal fistula

4.8.4.1.1 Conservative management

4.8.4.1.1.1 Spontaneous closure

The reported spontaneous closure rate is 13 ± 23% [727], although this applies largely to small fistulae (< 1 cm) [702, 728]. Hence, immediate management is usually by urinary catheterisation or diversion; however, within the first two weeks following fistula occurrence, surgical exploration and repair can be considered.

4.8.4.1.1.2 Pharmacotherapy

Several case reports describe a successful fistula closure rate following the induction of amenorrhoea by oestrogen, oestrogen/progesterone combinations or luteinising hormone releasing hormone analogues specifically for small (< 7 mm), uretero- or vesico-uterine fistulae following caesarean section [729-735]. One RCT comparing the efficacy of using fibrin glue compared to Martius flap inter-positioning (n = 14; < 4 cm and n = 5; > 5 cm) did not report significantly different outcomes between the two types of treatment [736].

4.8.4.1.1.3 Palliation and skin care

During the intervening period between diagnosis and repair, UI pads with the aim of prevention of skin complications related to chronic urinary leakage can be provided and the use of a barrier cream or local oestrogen can also be considered [737, 738].

4.8.4.1.1.4 Nutrition

Nutritional support is essential in patients with fistulae induced by malignant disease or radiotherapy [739], or following diversion surgery [739-741].

4.8.4.1.1.5 Physiotherapy

Early involvement of the physiotherapist in preoperative management and rehabilitation of fistula patients suffering from limb weakness, foot drop and limb contracture is essential [742, 743].

4.8.4.1.1.6 Antimicrobial therapy

Active infection in the genital or urinary tracts should be treated prior to surgical repair [744].

4.8.4.1.1.7 Counselling

Confident and realistic counselling by the surgeon is essential and the involvement of nursing staff or counsellors with experience of fistula patients is also desirable.

4.8.4.1.2 Surgical management

4.8.4.1.2.1 Timing of surgery

Findings from uncontrolled case series suggest no difference in success rates for early (within three weeks) or delayed (after three months) closure of VVF.

4.8.4.1.2.2 Surgical approaches

Vaginal procedures

There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis [727] and the more commonly used dissection and repair in layers or flap-splitting technique [745]. There are no data comparing their outcomes.

Abdominal procedures

Repair by the abdominal route is indicated when high fistulae are fixed at the vaginal vault and are inaccessible via a vaginal approach. A transvesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often although it is favoured by some using the laparoscopic approach. A combined transperitoneal and transvesical procedure may be utilised for fistula repair following caesarean section. There are no RCTs comparing abdominal and vaginal approaches. Results of secondary and subsequent repairs are not as successful as the initial repair [746].

A single RCT compared trimming of the fistula edge with no trimming. There was no difference in success rates but failed repairs in trimmed cases had larger recurrences than untrimmed cases, which were smaller [747].

Laparoscopic and robotic procedures

Small series (single figures) have reported using these techniques, but while laparoscopic repair is feasible with and without robotic assistance, it is not possible to compare outcomes with alternative surgical approaches.

Tissue interposition

Tissue flaps are often added as an additional layer of repair during VVF surgery. Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischaemic or obstetric fistulae, large fistulae, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high-level evidence that the use of such flaps improves outcomes for either complicated or uncomplicated VVF.

Postoperative management

There is no high-level evidence to support any particular practice in postoperative management but most reported series used catheter drainage for ≥ 10 days and longer periods in complex or radiation-associated fistulae (up to three weeks). The performance of postoperative cystography prior to catheter removal can miss a persistent fistula if not done with a micturition phase or if the fistula is located at the bladder neck.

4.8.4.1.3 Management of complications of vesico-vaginal fistulae

The complications of VVF repair are varied and can include:

- Persistence or recurrence of fistula;
- Persistence or recurrence of UI;
- Persistence of LUTS or occurrence of new LUTS, including *de novo* overactive bladder symptoms and/or SUI;
- Infections: wound and UTIs/urosepsis;
- Ureteric obstruction (ligation, fibrosis or injury);
- Bladder outlet obstruction (meatal stenosis, urethral stricture or bladder neck obstruction);
- Bladder contracture;
- Vaginal stenosis;
- Sexual dysfunction (vaginismus/dyspareunia);
- Rare complications (granulomas/diverticulum formation);
- Neurological complications (foot drop/neurogenic bladder);
- Psychological trauma (social isolation/divorce/mental illness);
- Infertility.

The literature on the treatment and management of complications of fistula repairs is scarce and is mostly experience-based. It is impossible to provide any specific evidence-based guidance.

4.8.4.2 Management of radiation fistulae

Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer [748]. Due to the wide field abnormality surrounding many radiotherapy-associated fistulae, approaches include, permanent urinary and/or faecal diversion [748, 749] or preliminary urinary and faecal diversion, with later undiversion in selected cases following reconstruction. In cases where life expectancy is deemed to be short, ureteric occlusion might be more appropriate.

4.8.4.3 Management of ureteric fistulae

4.8.4.3.1 General principles

Patients at higher risk of ureteric injury require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and recognise injury promptly. Immediate repair of any intraoperative injury should be performed by observing the principles of debridement, adequate blood supply and tension-free anastomosis with internal drainage using stents [750]. Delayed presentation of UUT injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvicalyceal system.

While there is no evidence to support the use of one surgical approach over another, there is consensus that repair should adhere to the standard principles of tissue repair and safe anastomosis, and be undertaken by an experienced team. Conservative management is possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< 2 weeks) or delayed (> 3 months) surgical repair when required [751]. Functional and anatomical imaging should be used to follow-up patients after repair to guard against development of ureteric stricture and deterioration in renal function.

4.8.4.3.2 Uretero-vaginal fistulae

Uretero-vaginal fistula occurring in the early postoperative phase predominantly after hysterectomy is the most frequent presentation of UUT fistulae in urological practice. An RCT in 3141 women undergoing open or laparoscopic gynaecological surgery found that prophylactic insertion of ureteric stents made no difference to the low risk (1%) of ureteric injury [752].

Endoscopic management is sometimes possible by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or ureteroscopic realignment [753]. However, the long-term success rate is unknown. If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, reimplantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration. As a last resort, nephrectomy may be considered, particularly in the context of a poorly functioning kidney and an otherwise normal contralateral kidney [754-758].

4.8.4.3.3 Management of urethro-vaginal fistulae

4.8.4.3.3.1 Aetiology

Although urethro-vaginal fistulae are rare, most of them in adults have an iatrogenic aetiology. Causes include surgical treatment of SUI with bulking agents or synthetic slings, surgery for urethral diverticulum and genital reconstruction. Irradiation and even conservative treatment of prolapse with pessaries can lead to formation of fistulae.

4.8.4.3.3.2 Diagnostic evaluation

Clinical vaginal examination, including the three-swab test, is often sufficient to diagnose UVF. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistulae. In cases of difficult diagnosis, VCUG or US can be useful. An 3D-MRI or CT scan is becoming utilised more widely to clarify anatomy [759, 760].

4.8.4.3.3.3 Surgical management

Choice of surgery will depend on the size, localisation, and aetiology of the fistula and the amount of tissue loss. Principles of reconstruction include identifying the fistula, creation of a plane between the vaginal wall and urethra, watertight closure of the urethral wall, eventual interposition of tissue, and closure of the vaginal wall.

One case series reported that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, and that an abdominal approach only led to successful closure in 58% of cases [761]. A vaginal approach required less operating time, had less blood loss and shorter hospitalisation.

Most authors have described surgical principles that are identical to those of VVF repair, and primary closure rates of 53–95.4% have been described. A series of 71 women, treated for UVF reported that 90.1% of fistulae were closed at the first vaginal intervention. Additionally, 7.4% were closed during a second vaginal intervention. Despite successful closure, SUI developed in 52% of cases. Stress urinary incontinence patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation or urethrotomy [762].

4.8.4.3.3.4 Flaps and neo-urethra

The simplest flap is a vaginal advancement flap to cover the urethral suture line. Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect, but can also be used to create a tubular neo-urethra [763, 764]. The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases, a transpubic approach has been used [765]. The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbo-cavernosus tissue can be incorporated in the pedicled flap and probably offers better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome SUI would occur postoperatively [766, 767].

4.8.4.3.3.5 Martius flap

In obstetrical fistula repair, the Martius labial bulbocavernosus muscle/fat flap was not found to have any benefit. However, the Martius flap is still considered by some to be an important adjunctive measure in the treatment of genitourinary fistulae for which additional bulking with well-vascularised tissue is needed [768]. The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomised studies [769]. The indications for Martius flap in the repair of UVF remain unclear.

4.8.4.3.3.6 Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors [770, 771].

4.8.4.3.3.7 Alternative approaches

An alternative retropubic retro-urethral technique has been described by Koriatim [772]. This approach allows a urethro-vesical flap tube to be fashioned to form a continent neo-urethra.

4.8.4.4 Summary of evidence and recommendations for the management of urinary fistula

Summary of evidence	**LE**
Spontaneous closure of surgical fistulae does occur, and appears more likely for small fistulae although it is not possible to establish the rate with any certainty.	3
There is no evidence that the timing of repair makes a difference to the chances of successful closure of a fistula.	3
There is no high-quality evidence of differing success rates for repair of VVFs by vaginal, abdominal, transvesical, and transperitoneal approaches.	3
A period of continuous bladder drainage may be crucial to successful fistula repair but there is no high-level evidence to support one regimen over another.	3
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting.	3
Post-radiation fistula	
Successful repair of irradiated fistulae may require prior urinary diversion and the use of non-irradiated tissues to effect repair.	3
Ureteric fistula	
Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery.	2
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase.	4
Urethro-vaginal fistula	
Urethro-vaginal fistula repair may be complicated by SUI, urethral stricture and urethral shortening, which may necessitate long-term follow-up.	3

Recommendations	**Strength rating**
General	
When reporting on outcomes after fistula repair, authors should make a clear distinction between fistula closure rates and postoperative urinary incontinence rates and the time at which the follow-up was organised.	Strong
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	Strong

Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs postoperatively, or if drainage fluid contains high levels of creatinine.	Strong
Use three-dimensional imaging techniques to diagnose and localise urinary fistulae, particularly in cases with negative direct visual inspection or cystoscopy.	Weak
Manage upper urinary tract fistulae initially by conservative or endoluminal techniques where such expertise and facilities exists.	Weak
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills and experience to select an appropriate procedure for each patient.	Weak
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to, and following, fistula repair.	Weak
Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	Weak
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: ten to fourteen days for simple and/or post-surgical fistulae; fourteen to 21 days for complex and/or post-radiation fistulae).	Weak
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	Weak
Use interposition graft when repair of radiation-associated fistulae is undertaken.	Weak
Repair persistent uretero-vaginal fistulae by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence.	Weak
Urethro-vaginal fistulae should preferably be repaired by a vaginal approach.	Weak

4.9 Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion composed of the entire urethral wall or only the urethral mucosa, situated between the periurethral tissues and the anterior vaginal wall.

*4.9.1 **Epidemiology, aetiology, pathophysiology***

Urethral diverticulum is an uncommon condition with an estimated prevalence of 1–6%. A prevalence of up to 10% was reported among women with LUTS attending a tertiary referral centre [773]. However, as many patients are asymptomatic or misdiagnosed, the true incidence is unknown [774-776]. Given the rarity of the condition, most published series are small and single institutional. Urethral diverticulum is thought to arise from repeated obstruction, infection, and subsequent rupture of periurethral glands into the urethral lumen, resulting in an epithelialised cavity that communicates with the urethra [774].

Iatrogenic damage to the urethra may also play a role, as up to 20% of women with urethral diverticula are noted to have a history of urethral surgery, dilation, or traumatic delivery [774, 777]. Iatrogenic urethral diverticula formation associated with synthetic suburethral sling has also been reported [778-780].

*4.9.2 **Classification***

Table 7: Classification system for female urethral diverticula based on characteristics*

Localisation	Mid-urethral Distal Proximal Full length
Configuration	Single Multi-loculated Saddle shaped
Communication	Mid-urethral No communication visualised Distal Proximal
Continence	Stress urinary incontinence Continent Post-void dribble Mixed incontinence

**Limited LNS C3 classification of urethral diverticula [777, 781, 782].*

*4.9.3 **Diagnostic evaluation***

The commonly encountered symptoms for urethral diverticulum such as pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or UI [783], are common to many other LUT dysfunctions. Consequently, there is no pathognomonic cluster of symptoms to identify urethral diverticulum. Many patients with urethral diverticulum are asymptomatic. However, urethral diverticulum often presents with a palpable urethral mass. It may be possible to express a purulent exudate from the urethra. Occasionally a stone may develop within the diverticulum.

Urethral diverticulum can be diagnosed by physical examination, VCUG and MRI. Other investigations include urethrocystoscopy, endocavitary (often transvaginal or sometimes transurethral) pelvic floor US and double balloon urethrography.

No robust diagnostic accuracy studies have addressed the question of the best test to confirm the diagnosis in women with clinical suspicion of urethral diverticulum. However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than VCUG [784] and determines the size and extent of urethral diverticulum more accurately. A case series of 60 patients reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI was 100%, 83%, 92% and 100%, respectively [785]. Another case series reported 100% specificity and sensitivity of MRI in 60 patients [786]. However, a case series of 41 patients reported a 25% discrepancy between MRI and surgical findings [787]. Endoluminal MRI with either a vaginal or rectal coil may provide even better image quality than simple MRI [788].

Magnetic resonance imaging is the gold standard for the diagnosis and planning of surgical repair. Magnetic resonance imagine is also useful in diagnosing diverticular inflammation or tumour [789, 790].

Urethrocystoscopy can be used to visualise the ostia of the diverticula. Knowledge of the ostias' location and number can assist with surgical planning since they need to be closed after diverticulectomy. However, given the challenges of urethroscopy in women, the ostia are only seen in 42% of cases [783].

If VCUG is performed, antero-posterior and lateral images are required to optimally characterise the configuration of the diverticulum. There is a high risk of false negatives since the ostia of the diverticula must be patent and the patients must be able to void during the study. In more complex diverticula where there is septation, the entire diverticulum may not be visualised underestimating its complexity or size [791]. The sensitivity of VCUG is 73.5% which is significantly worse than MRI [783].

Ultrasound can be performed transabdominally, transvaginally or transperineally to identify the diverticulum. In particular, the transvaginal approach allows imaging of the urethra from the meatus to the bladder neck in several planes and can identify the number, size, location and contents of the diverticulum. This technique is challenging and requires a skilled ultrasonographer. Additionally, the probe can compress the urethra, causing distortion [791]. A meta-analysis reported that US of any kind had a sensitivity of 82.0%, which was inferior to that of MRI [791]. However, a recent publication on translabial US reported a sensitivity of 95% [792]; therefore, this approach may be explored further by researchers in the future.

For patients who cannot undergo MRI and those in whom the ostia cannot be seen on cystoscopy, double balloon urethrography is an option. Sensitivity of 94.7% has been reported, which is comparable to that of MRI. The technique uses positive pressure to force contrast medium into the diverticular sac between two balloons; one placed in the bladder and one outside the ostium of the diverticulum. It is technically difficult to achieve a seal sufficient to create a closed urethral space and avoid contrast medium leaking around the catheter. The procedure can be painful for the patient and carries a risk of UTI. An experienced radiologist is required as well as specialised equipment. Given the current popularity of other imaging modalities, many units may not have access to this technique [791].

4.9.3.1 Associated voiding dysfunction

Although the presentation of urethral diverticulum is often non-specific and variable, urethral diverticulum can be associated with voiding dysfunction and SUI or urgency UUI.

One recent series reported SUI in 60% of patients with urethral diverticulum [793]. Urethral diverticulum is most often located at the level of the mid-urethra. This location often overlaps with the external sphincter. However, urethral diverticulum may also extend proximally toward the bladder neck in the vicinity of the proximal sphincter mechanism. This morphology may, in part, explain the association between urethral diverticulum and SUI, with potentially more proximal lesions at risk for postoperative SUI [794].

Urethral diverticulum may also be associated with BOO due to the mass effect of the urethral diverticulum, urinary retention, or urgency and UUI [795]. Pain and dysuria associated with urethral diverticulum may also result in acquired voiding dysfunction.

Pressure–flow studies may have a role in the preoperative assessment of patients with urethral diverticula and coexisting voiding dysfunction or SUI [776, 796-798]. Indeed, urodynamics may evaluate coexisting detrusor dysfunction or document the presence of SUI or obstruction prior to repair [799, 800].

Urethral pressure profilometry has also been used in the assessment or diagnosis of urethral diverticulum, noting a biphasic pattern, or pressure drop at the level of the lesion [796, 798, 801]. Video-urodynamics may be helpful in differentiating SUI from paradoxical UI due to fluid accumulation in the urethral diverticulum. Additionally, resting and straining images obtained during fluoroscopic imaging may document an open bladder neck at rest. This may be a consideration in some patients with an extensive urethral diverticulum at the level of the mid-urethra, and potential implications for postoperative UI due to compromise of both sphincter mechanisms.

*4.9.4 **Disease management***

For women with minimal symptoms who would prefer to avoid invasive treatment, conservative management can be considered. Patients should be warned of the small risk of cancer (1–6%) within the diverticulum [802, 803].

4.9.4.1 Surgical treatment

No RCTs have investigated the effectiveness of surgery in women who have a bothersome urethral diverticulum. Thorough evaluation of the anatomy of the diverticulum is essential in planning reconstructive surgery.

There are three surgical approaches to treatment of diverticulum: marsupialisation, endoscopic incision, and curative treatment with diverticulectomy.

Surgical removal is the most commonly reported treatment in contemporary case series. The principles of successful transvaginal diverticulectomy are to: dissect a well-vascularised vaginal flap; preserve the periurethral fascia for closure; remove all the diverticular wall; excise the ostium and close the urethra in a watertight fashion; close the incision in a multilayered fashion with no overlapping suture lines; and preservation or creation of continence.

The decision to use a labial fat pad flap, commonly known as a Martius flap, varies, and the flap is used more frequently in the following situations: recurrent cases, large urethral defects or for deficient vaginal flaps for closure [777, 781] transection of the urethra required for access to a circumferential diverticulum [790] or in the case of complex configuration [795], and if there is a planned future sling procedure required for UI to facilitate the dissection at that time [777].

Marsupialisation involves incision into the mass on the vaginal side to drain the infected contents. The wall is sutured open with absorbable suture to allow drainage and prevent reaccumulation of infectious materials. This approach leaves the cystic structure in place and can theoretically cause a urethro-vaginal fistula because there is communication with the diverticular ostium, but it is a rapid procedure with little dissection required. This approach has been advocated in pregnant patients to decompress the diverticulum and allow safe vaginal delivery. A small case series suggested that 75% of pregnant women with urethral diverticula managed expectantly eventually required postpartum surgery [804].

Endoscopic incision is a rarely reported treatment option [805, 806]. This procedure involves finding the narrow neck of the ostium and incising it with a resectoscope. This unroofing of the diverticulum transforms the narrow communication with the urethra that causes symptoms when it becomes obstructed into a wide-mouthed sac that drains freely.

4.9.4.2 Management of concomitant stress urinary incontinence

Many women present with concomitant SUI and urethral diverticulum, and may request both conditions to be simultaneously treated. A meta-analysis reported that diverticulectomy cured SUI even without a concomitant anti-incontinence procedure. However, no data regarding symptom severity were given and it could be assumed that many of these cured patients had less-severe UI before surgery [783]. Therefore, additional surgical correction may be required [794, 806]. However, there is no consensus on appropriate timing of surgical management of these two conditions. Thus, patients with symptomatic bothersome SUI in

association with urethral diverticulum may be offered simultaneous anti-UI surgery. Although historical series have shown good results with concomitant bladder neck suspension [800], more contemporary series have utilised pubovaginal fascial slings, with satisfactory outcomes [807-810]. Synthetic MUS are not recommended as a concomitant anti-UI procedure at the time of urethral diverticulectomy [811]. Synthetic material adjacent to a fresh suture line following diverticulectomy in the setting of potentially infected urine may place the patient at higher risk for subsequent urethral erosion and vaginal extrusion of the sling material, as well as urethro-vaginal fistula formation and foreign body granuloma formation.

Transvaginal urethral diverticulectomy has a high success rate (defined by being dry) of 84–98%, with a reoperation rate of 2–13% after primary repair during a mean follow-up of twelve to 50 months [774, 777, 794, 812]. The resolution of symptoms after surgery has been reported to reach 68.8% but less than half of studies comment on symptom improvement [813]. One case series reported that storage symptoms decreased significantly postoperatively from 60% to 16% following surgery for urethral diverticulum [794]. Other series with long-term follow-up, however, have demonstrated rates of postoperative urgency of 54% [814], and *de novo* UUI in 36% of patients [806]. Such postoperative symptoms indicate persistence of urethral diverticulum, recurrence of urethral diverticulum, or *de novo* overactive bladder syndrome or urethral obstruction.

Early common postoperative complications include: UTI (0–39%), *de novo* SUI (3.8–33%), and *de novo* urinary retention (0–9%), especially in the setting of concomitant placement of an autologous pubovaginal sling [774, 777, 794, 812]. Delayed complications such as urethral stricture are reported in 0–5.2% of cases [774, 777, 806, 812]. Urethro-vaginal fistula is a devastating complication presenting in 0.9–8.3% of cases [815]. A distal fistula located beyond the sphincteric mechanism can present with split urinary stream or vaginal voiding and may not require repair. However, a fistula located anywhere from the mid-urethra to the bladder neck may result in UI. These patients should undergo repair with consideration of an adjuvant tissue flap, such as a Martius flap, to aid in closure. The timing of the fistula repair is not well defined, with a delay of three to six months after the initial repair being a good balance between patient discomfort and optimal tissue quality. Rare complications include: distal urethral necrosis, bladder injury, urethral injury, ureteric injury, and vaginal scarring or narrowing with consequent dyspareunia [815].

One case series reported a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticula within one year [781], Ingber *et al*., found a 10.7% recurrence rate in 122 women undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [814] or radiation. Recurrent urethral diverticulum following initial successful urethral diverticulectomy may occur as a result of a new infection or traumatic insult such as childbirth, a new urethral diverticulum, or recurrence of the original lesion. Recurrence of urethral diverticulum may be due to incomplete removal of the urethral diverticulum, inadequate closure of the urethra, residual dead space (circumferential diverticula), or other technical factors. Repeat urethral diverticulectomy represents a unique challenge due to altered anatomy, scarring, and difficulty identifying proper anatomical planes.

Stress urinary incontinence can be worsened or occur *de novo* after diverticulectomy. This is most likely due to sphincteric damage from the dissection or scarification preventing urethral closure. *De novo* SUI (10.6% of women) seems to be more common in proximal and large (> 30 mm) diverticula [794]. However, Lee *et al*., noted at least some *de novo* SUI in 49% of patients following urethral diverticulectomy; most of which was minor and did not require additional therapy [816]. Only 10% of these individuals underwent subsequent SUI surgery. Treatment for SUI after diverticulectomy is not well described in the literature. The most commonly reported operation is an autologous pubovaginal sling [805] followed by retropubic suspension [806]. However, there are two reported cases of synthetic mesh sling to treat SUI, without mesh complications [781, 794], but this is controversial.

4.9.4.3 Pathological findings

Most urethral diverticula are lined with squamous cells, urothelium or columnar epithelium [777, 817, 818]. In a meta-analysis, there was a high prevalence of chronic or acute inflammation (68.6%) and the most commonly reported lesions were nephrogenic metaplasia, which occurred in 8% of cases. Diverticula may undergo neoplastic alterations (6%), including invasive adenocarcinoma [819], followed by squamous cell carcinoma in 0.7%. It is unknown if the diverticulum forms first and then transforms into a malignancy or if the malignancy develops first. These malignancies are treated in a similar fashion to urethral cancer in women.

4.9.5 *Summary of evidence and recommendations for urethral diverticulum*

Summary of evidence	LE
Magnetic resonance imaging has the best sensitivity and specificity for the diagnosis of urethral diverticulum.	3
Surgical removal of symptomatic urethral diverticulum provides good long-term results; however, women should be counselled of the risk of recurrence and *de novo* SUI.	3

Recommendations	Strength rating
Offer surgical removal of symptomatic urethral diverticulum.	Weak
If conservative treatment is adopted, warn patients of the small (1–6%) risk of cancer developing within the diverticulum.	Weak
Carefully question and investigate patients for coexisting voiding dysfunction and urinary incontinence (UI).	Strong
Following appropriate counselling, address bothersome stress urinary incontinence at the time of urethral diverticulectomy with concomitant non-synthetic sling.	Weak
Counsel patients regarding the possibility of *de novo* or persistent LUTS including UI, despite technically successful urethral diverticulectomy.	Strong

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6. CONFLICT OF INTEREST

All members of the Non-neurogenic Female LUTS Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/non-neurogenic-female-luts/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

7. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

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1. INTRODUCTION

1.1 Aim and objectives

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and have a substantial economic burden. The present Guidelines offer practical evidence-based guidance on the assessment and treatment of men aged 40 years or older with various non-neurogenic benign forms of LUTS. The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH). The term BPH is now regarded as inappropriate as it is Benign Prostatic Obstruction (BPO) that is treated if the obstruction is a significant cause of a man's LUTS. It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Non-neurogenic Male LUTS Guidelines Panel consists of an international group of experts with urological and clinical epidemiological backgrounds. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.4 Publication history

The Non-neurogenic Male LUTS Guidelines was first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. All sections of the 2022 Male LUTS Guidelines have been fully updated.

2. METHODS

2.1 Introduction

For the 2022 Management of Non-Neurogenic Male LUTS Guidelines, new and relevant evidence was identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic Male LUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e., systematic reviews (SRs) with meta-analysis, Randomised Controlled Trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between May 1st 2019 and May 1st, 2021. A total of 2,853 unique records were identified, retrieved, and screened for relevance.

In addition, a new section, 5.6 Management of male urinary incontinence, has been added to the Guidelines. This topic was originally addressed in the now discontinued EAU Guidelines on Urinary Incontinence in Adults [1]. As with the overall Guidelines a broad and comprehensive literature search, limited to studies representing high levels of evidence and published in the English language was performed for this section. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame from May 2017, the previous update cut-off of the EAU Urinary Incontinence Guidelines and June 24th, 2021. A total of 1,054 unique records were identified, retrieved, and screened for relevance. Detailed search strategies are available online: http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/supplementary-material.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [2, 3]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The Non-Neurogenic Male LUTS Guidelines were peer reviewed prior to publication in 2016. The newly added section on management of urinary incontinence in males was peer reviewed prior to the publication in 2022.

2.3 Patients to whom the guidelines apply

Recommendations apply to men aged 40 years or older who seek professional help for LUTS in various non-neurogenic and non-malignant conditions such as BPO, detrusor overactivity (DO)/overactive bladder (OAB), or nocturnal polyuria. Men with other associated factors relevant to LUT disease (e.g., concomitant neurological diseases, young age, prior LUT disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following sections. EAU Guidelines on Neuro-Urology, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [6], they are prevalent, cause bother and impair QoL [7-10]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [11]. Lower urinary tract symptoms are strongly associated with ageing [7, 8], associated costs and burden are therefore likely to increase with future demographic changes [8, 12]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [13]. In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events [14].

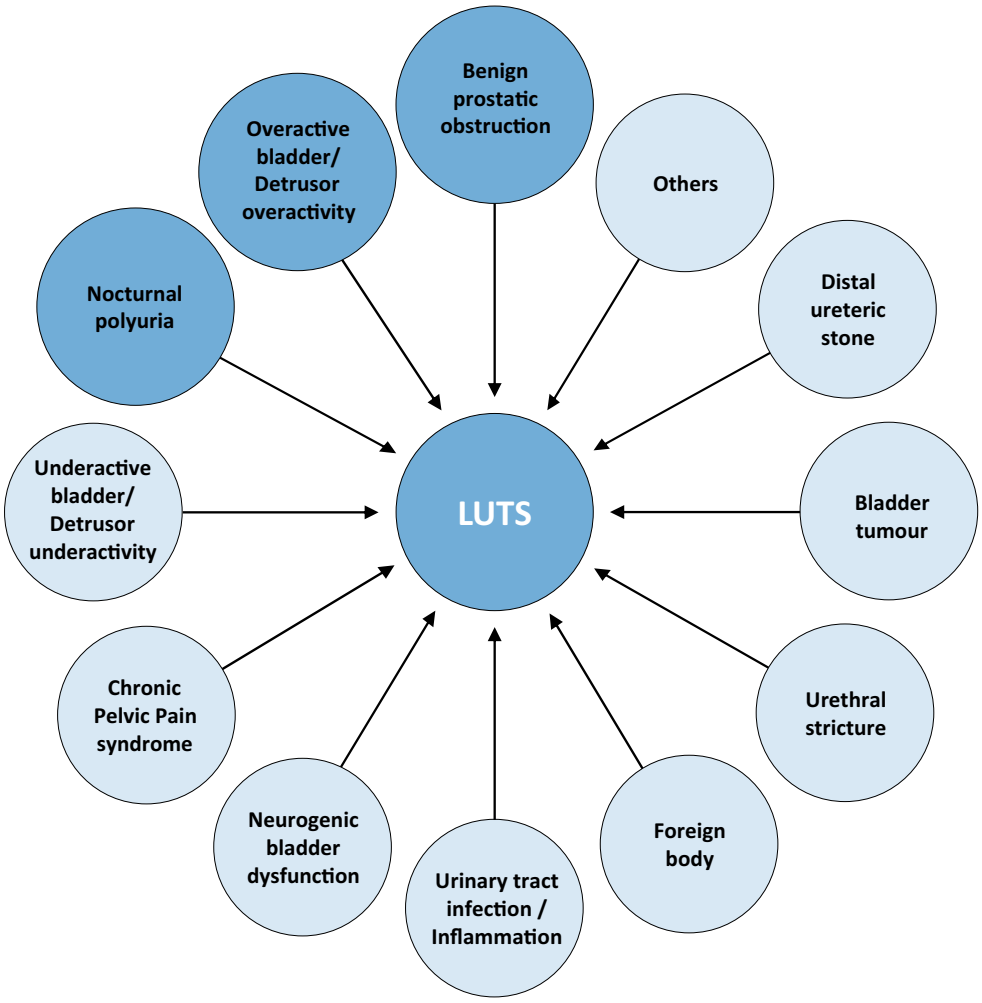
Most elderly men have at least one LUTS [8]; however, symptoms are often mild or not very bothersome [10, 11, 15]. Lower urinary tract symptoms can progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [8]. Lower urinary tract symptoms have traditionally been related to bladder outlet obstruction (BOO), most frequently when histological BPH progresses through benign prostatic enlargement (BPE) to BPO [6, 9]. However, increasing numbers of studies have shown that LUTS are often unrelated to the prostate [8, 16]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity (DU)/underactive bladder (UAB), as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [16]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [17, 18]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [8].

The definitions of the most common conditions related to male LUTS are presented below:

- Acute retention of urine is defined as a painful, palpable or percussible bladder, when the patient is unable to pass any urine [6].
- Chronic retention of urine is defined as a non-painful bladder, which remains palpable or percussible after the patient has passed urine. Such patients may be incontinent [6].
- Bladder outlet obstruction is the generic term for obstruction during voiding and is characterised by increasing detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow-rate and detrusor pressure [6].
- Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [6]. In the Guidelines the term BPO or BOO is used as reported by the original studies.
- Benign prostatic hyperplasia is a term used (and reserved) for the typical histological pattern, which defines the disease.
- Detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [6]. Detrusor overactivity is usually associated with OAB syndrome characterised by urinary urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [19].
- Detrusor underactivity during voiding is characterised by decreased detrusor voiding pressure leading to a reduced urine flow rate. Detrusor underactivity causes OAB syndrome which is characterised by voiding symptoms similar to those caused by BPO [20].

Figure 1 illustrates the potential causes of LUTS. In any man complaining of LUTS, it is common for more than one of these factors to be present.

Figure 1: Causes of male LUTS



4. DIAGNOSTIC EVALUATION

Tests are useful for diagnosis, monitoring, assessing the risk of disease progression, treatment planning, and the prediction of treatment outcomes. The clinical assessment of patients with LUTS has two main objectives:

- to identify the differential diagnoses, since the origin of male LUTS is multifactorial, the relevant EAU Guidelines on the management of applicable conditions should be followed;
- to define the clinical profile (including the risk of disease progression) of men with LUTS in order to provide appropriate care.

4.1 Medical history

The importance of assessing the patient's history is well recognised [21-23]. A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, current medication, lifestyle habits, emotional and psychological factors must be reviewed. The Panel recognises the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no definite link between LUTS and prostate cancer (PCa) [24, 25].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see section 4.2) should be obtained to objectify and quantify LUTS. Bladder diaries or frequency volume charts (FVC) are particularly beneficial when assessing patients with nocturia and/or storage symptoms (see section 4.3). Sexual function should also be assessed, preferably with validated symptom questionnaires such as the International Index of Erectile Function (IIEF) [26].

Summary of evidence	LE
A medical history is an integral part of a patient's medical evaluation.	4
A medical history aims to identify the potential causes of LUTS as well as any relevant comorbidities and to review the patient's current medication and lifestyle habits.	4

Recommendation	Strength rating
Take a complete medical history from men with LUTS.	Strong

4.2 Symptom score questionnaires

All published guidelines for male LUTS recommend using validated symptom score questionnaires [21, 23]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [27-33]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant; however, they are not disease-, gender-, or age-specific. A SR evaluating the diagnostic accuracy of individual symptoms and questionnaires, compared with urodynamic studies (the reference standard), for the diagnosis of BOO in males with LUTS found that individual symptoms and questionnaires for diagnosing BOO were not significantly associated with one another [34].

4.2.1 The International Prostate Symptom Score (IPSS)

The IPSS is an eight-item questionnaire, consisting of seven symptom questions and one QoL question [28]. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

4.2.2 The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)

The ICIQ-MLUTS was created from the International Continence Society (ICS) male questionnaire. It is a widely used and validated patient completed questionnaire including incontinence questions and bother for each symptom [29]. It contains thirteen items, with subscales for nocturia and OAB, and is available in seventeen languages.

4.2.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS [32] is a symptom score used mainly in Denmark and Finland. The DAN-PSS also has questions on incontinence and measures the bother of each individual LUTS.

Summary of evidence	LE
Symptom questionnaires are sensitive to symptom changes.	3
Symptom scores can quantify LUTS and identify which types of symptoms are predominant; however, they are not disease-, gender-, or age-specific.	3

Recommendation	Strength rating
Use a validated symptom score questionnaire including bother and quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment.	Strong

4.3 Frequency volume charts and bladder diaries

The recording of volume and time of each void by the patient is referred to as a FVC. Inclusion of additional information such as fluid intake, use of pads, activities during recording, or which grades symptom severity and bladder sensation is termed a bladder diary [6]. Parameters that can be derived from the FVC and bladder diary include day-time and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index), and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Likewise, circumstantial influence and intra-individual variation cause FVC parameters to fluctuate, though there is comparatively little data [35, 36]. The FVC/bladder diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [37-39]. The use of FVCs may cause a 'bladder training effect' and influence the frequency of nocturnal voids [40].

The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [41]. A SR of the available literature recommended FVCs should continue for three or more days [42]. The ICIQ-Bladder diary (ICIQ-BD) is the only diary that has undergone full validation [43].

Summary of evidence	LE
Frequency volume charts (FVC) and bladder diaries provide real-time documentation of urinary function and reduce recall bias.	3
Three- and seven-day FVCs provide reliable measurement of urinary symptoms in patients with LUTS.	2b

Recommendations	Strength rating
Use a bladder diary to assess male LUTS with a prominent storage component or nocturia.	Strong
Tell the patient to complete a bladder diary for at least three days.	Strong

4.4 Physical examination and digital-rectal examination

Physical examination particularly focusing on the suprapubic area, the external genitalia, the perineum, and lower limbs should be performed. Urethral discharge, meatal stenosis, phimosis, and penile cancer must be excluded.

4.4.1 Digital-rectal examination and prostate size evaluation

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but the correlation to prostate volume is poor. Quality-control procedures for DRE have been described [44]. Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE. Underestimation of prostate volume by DRE increases with increasing TRUS volume, particularly where the volume is > 30 mL [45]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [46]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < 50 mL [47].

Summary of evidence	LE
Physical examination is an integral part of a patient's medical evaluation.	4
Digital-rectal examination can be used to assess prostate volume; however, the correlation to actual prostate volume is poor.	3

Recommendation	Strength rating
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	Strong

4.5 Urinalysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions, such as urinary tract infections (UTI), microhaematuria and diabetes mellitus. If abnormal findings are detected further tests are recommended according to other EAU Guidelines, e.g., Guidelines on urinary tract cancers and urological infections [48-51].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [52, 53]. There is limited evidence, but general expert consensus suggests that the benefits outweigh the costs

[54]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has been questioned [55].

Summary of evidence	LE
Urinalysis (dipstick or sediment) may indicate a UTI, proteinuria, haematuria or glycosuria requiring further assessment.	3
The benefits of urinalysis outweigh the costs.	4

Recommendation	Strength rating
Use urinalysis (by dipstick or urinary sediment) in the assessment of male LUTS.	Strong

4.6 Prostate-specific antigen

*4.6.1 **Prostate-specific angtigen and the prediction of prostatic volume***

Pooled analysis of placebo-controlled trials of men with LUTS and presumed BPO showed that prostate-specific antigen (PSA) has a good predictive value for assessing prostate volume, with areas under the curve (AUC) of 0.76-0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively [56].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [57]. A PSA threshold value of 1.5 ng/mL could best predict a prostate volume of > 30 mL, with a positive predictive value (PPV) of 78%. The prediction of prostate volume can also be based on total and free PSA. Both PSA forms predict the TRUS prostate volume (± 20%) in > 90% of the cases [58, 59].

*4.6.2 **Prostate-specific angtigen and the probability of PCa***

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [60]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient.

*4.6.3 **Prostate-specific angtigen and the prediction of BPO-related outcomes***

Serum PSA is a stronger predictor of prostate growth than prostate volume [61]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Q_{max}) [62]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [63, 64]. In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPO-related surgery [65, 66]. An equivalent link was also confirmed by the Olmsted County Study. The risk for treatment was higher in men with a baseline PSA of > 1.4 ng/mL [67]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The PPV of PSA for the detection of BPO was recently shown to be 68% [68]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [69].

Summary of evidence	LE
Prostate-specific antigen (PSA) has a good predictive value for assessing prostate volume and is a strong predictor of prostate growth.	1b
Baseline PSA can predict the risk of AUR and BPO-related surgery.	1b

Recommendations	Strength rating
Measure prostate-specific antigen (PSA) if a diagnosis of prostate cancer will change management.	Strong
Measure PSA if it assists in the treatment and/or decision-making process.	Strong

4.7 Renal function measurement

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention are more prevalent in patients with signs or symptoms of BPO [70]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [71].

One study reported that 11% of men with LUTS had renal insufficiency [70]. Neither symptom score nor QoL was associated with the serum creatinine level. Diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Comiter *et al.,* [72] reported that non-neurogenic voiding

dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.,* [73] concluded that only those with an elevated creatinine level require investigational ultrasound (US) of the kidney.

In the Olmsted County Study community-dwelling men there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [74]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [75]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [76]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [77].

Summary of evidence	LE
Decreased Q_{max} and a history of hypertension and/or diabetes are associated with CKD in patients who present with LUTS.	3
Patients with renal insufficiency are at an increased risk of developing post-operative complications.	3

Recommendation	Strength rating
Assess renal function if renal impairment is suspected based on history and clinical examination, or in the presence of hydronephrosis, or when considering surgical treatment for male LUTS.	Strong

4.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function/DU [78, 79]. Using a PVR threshold of 50 mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the prediction of BOO [80]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although it may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom progression [65, 66].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [81]. This is of particular importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPO-related invasive therapy in patients on α1-blockers or WW [82]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established; this is a research priority.

Summary of evidence	LE
The diagnostic accuracy of PVR measurement, using a PVR threshold of 50 mL, has a PPV of 63% and a NPV of 52% for the prediction of BOO.	3
Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR.	3

Recommendation	Strength rating
Measure post-void residual in the assessment of male LUTS.	Weak

4.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Q_{max} and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. As Q_{max} is prone to within-subject variation [83, 84], it is useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. A threshold Q_{max} of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% [85]. If Q_{max} is > 15 mL/s, physiological compensatory processes mean that BOO cannot be excluded. Low Q_{max} can arise as a consequence of BOO [86], DU or an under-filled bladder [87]. Therefore, it is limited as a diagnostic test as it is unable to discriminate between the underlying mechanisms. Specificity can be improved by repeated flow rate testing. Uroflowmetry can be used for monitoring treatment outcomes [88] and correlating symptoms with objective findings.

Summary of evidence	LE
The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. Specificity can be improved by repeated flow rate testing.	2b

Recommendations	Strength rating
Perform uroflowmetry in the initial assessment of male LUTS.	Weak
Perform uroflowmetry prior to medical or invasive treatment.	Strong

4.10 Imaging

*4.10.1 **Upper urinary tract***

Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [73, 89-91]. Several arguments support the use of renal ultrasound (US) in preference to intravenous urography. Ultrasound allows for better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, no radiation dose and less side effects [89]. Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.

Summary of evidence	LE
Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population.	3
Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.	4

Recommendation	Strength rating
Perform ultrasound of the upper urinary tract in men with LUTS.	Weak

*4.10.2 **Prostate***

Imaging of the prostate can be performed by transabdominal US, TRUS, computed tomography (CT), and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by transabdominal (suprapubic) US or TRUS [89].

4.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e., open prostatectomy (OP), enucleation techniques, transurethral resection, transurethral incision of the prostate (TUIP), or minimally invasive therapies. It is also important prior to treatment with 5α-reductase inhibitors (5-ARIs). Prostate volume predicts symptom progression and the risk of complications [91].

Transrectal US is superior to transabdominal volume measurement [92, 93]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach since medial lobe presence can be a contraindication for some minimally invasive treatments (see section 5.3).

Summary of evidence	LE
Assessment of prostate size by TRUS or transabdominal US is important for the selection of interventional treatment and prior to treatment with 5-ARIs.	3

Recommendations	Strength rating
Perform imaging of the prostate when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	Weak
Perform imaging of the prostate when considering surgical treatment.	Strong

*4.10.3 **Voiding cysto-urethrogram***

Voiding cysto-urethrogram (VCUG) is not recommended in the routine diagnostic work-up of men with LUTS, but it may be useful for the detection of vesico-ureteral reflux, bladder diverticula, or urethral pathologies. Retrograde urethrography may additionally be useful for the evaluation of suspected urethral strictures.

4.11 Urethrocystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation. The evaluation of a prostatic middle lobe with urethrocystoscopy should be performed when considering interventional treatments for which the presence of middle lobe is a contraindication.

A prospective study evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [94]. The pre-operative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had a reduced Q_{max}.

Another study showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV), and the pre-operative Q_{max} value in 39 symptomatic men aged 53-83 years [95]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [96]. The authors noted a correlation between cystoscopic appearance (grade of bladder trabeculation and urethral occlusion) and urodynamic indices, DO and low compliance. It should be noted, however, that BOO was present in 15% of patients with normal cystoscopic findings, while 8% of patients had no obstruction, even in the presence of severe trabeculation [96].

Summary of evidence	LE
Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.	3
None of the studies identified a strong association between the urethrocystoscopic and urodynamic findings.	3

Recommendation	Strength rating
Perform urethrocystoscopy in men with LUTS prior to minimally invasive/surgical therapies if the findings may change treatment.	Weak

4.12 Urodynamics

In male LUTS, the most widespread invasive urodynamic techniques employed are filling cystometry and pressure flow studies (PFS). The major goal of urodynamics (UDS) is to explore the functional mechanisms of LUTS, to identify risk factors for adverse outcomes and to provide information for shared decision-making. Most terms and conditions (e.g. DO, low compliance, BOO/BPO, DU) are defined by urodynamic investigation.

*4.12.1 **Diagnosing bladder outlet obstruction***

Pressure flow studies are used to diagnose and define the severity of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outlet obstruction/BPO has to be differentiated from DU, which exhibits decreased detrusor pressure during voiding in combination with decreased urinary flow rate [6].

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [97, 98]. In men with LUTS attributed to BPO, DO was present in 61% and independently associated with BOO grade and ageing [97].

The prevalence of DU in men with LUTS is 11-40% [99, 100]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [101, 102]. An RCT investigated whether urodynamics would reduce surgery without increasing urinary symptoms. The UPSTREAM study was a non-inferiority, RCT in men with bothersome LUTS, in whom surgery was an option, in 26 hospitals in England. From the 820 men, 153/408 (38%) were in the UDS arm and received surgery compared with 138/384 (36%) in the routine care (RC) arm. A total of 428 adverse events were recorded, with related events similar in both arms and eleven unrelated deaths. The UDS group was non-inferior to the RC group for IPSS, but UDS did not reduce surgical rates. The authors concluded that routine use of UDS in the evaluation of uncomplicated LUTS has a limited role and should be used selectively [103]. If urodynamic investigation is performed, a rigorous quality control is mandatory [104].

Due to the invasive nature of the test, a urodynamic investigation is generally only offered if conservative treatment has failed. The Guidelines Panel attempted to identify specific indications for PFS based on age, findings from other diagnostic tests and previous treatments. The Panel allocated a different degree of obligation for PFS in men > 80 years and men < 50 years, which reflects the lack of evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s, although the Panel recognised that with a Q_{max} < 10 mL/s, BOO is likely and PFS is not necessarily needed.

Patients with neurological disease, including those with previous radical pelvic surgery, should be assessed according to the EAU Guidelines on Neuro-Urology [105].

*4.12.2 **Videourodynamics***

Videourodynamics provides additional anatomical and functional information and may be recommended if the clinician considers this is needed to understand the pathophysiological mechanism of an individual patient's LUTS.

Summary of evidence	LE
Urodynamics is not a test for routine use prior to prostate surgery for all patients	3

Recommendations	Strength rating
Perform pressure-flow studies (PFS) only in individual patients for specific indications prior to invasive treatment or when further evaluation of the underlying pathophysiology of LUTS is warranted.	Weak
Perform PFS in men who have had previous unsuccessful (invasive) treatment for LUTS.	Weak
Perform PFS in men considering invasive treatment who cannot void > 150 mL.	Weak
Perform PFS when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s.	Weak
Perform PFS when considering invasive therapy in men with bothersome, predominantly voiding LUTS with a post void residual > 300 mL.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged > 80 years.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged < 50 years.	Weak

4.13 Non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS

4.13.1 Prostatic configuration/intravesical prostatic protrusion

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [106]. The PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward one as the prostate becomes more circular. The sensitivity of PCAR was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [106].

Ultrasound measurement of intravesical prostatic protrusion (IPP) assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with a bladder volume of 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is > 10 mm.

Intravesical prostatic protrusion correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [107]. Intravesical prostatic protrusion may also correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [108]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter after AUR [109, 110]. However, no information with regards to intra- or inter-observer variability and learning curve is yet available. Therefore, whilst IPP may be a feasible option to infer BPO in men with LUTS, the role of IPP as a non-invasive alternative to PFS in the assessment of male LUTS remains under evaluation.

4.13.2 Bladder/detrusor wall thickness and ultrasound-estimated bladder weight

For bladder wall thickness (BWT) assessment, the distance between the mucosa and the adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the detrusor sandwiched between the mucosa and adventitia [111].

A correlation between BWT and PFS parameters has been reported. A threshold value of 5 mm at the anterior bladder wall with a bladder filling of 150 mL was best at differentiating between patients with or without BOO [112]. Detrusor wall thickness at the anterior bladder wall with a bladder filling > 250 mL (threshold value for BOO > 2 mm) has a PPV of 94% and a specificity of 95%, achieving 89% agreement with PFS [73]. Threshold values of 2.0, 2.5, or 2.9 mm for DWT in patients with LUTS are able to identify 81%, 89%, and 100% of patients with BOO, respectively [113].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or Q_{ave} of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. One study could not demonstrate any difference in BWT between patients with normal UDS, BOO or DO. However, the study did not use a specific bladder filling volume for measuring BWT [114]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [115]. Measurement of BWT/DWT is therefore not recommended for the diagnostic work-up of men with LUTS.

Ultrasound-estimated bladder weight (UEBW) may identify BOO with a diagnostic accuracy of 86% at a cut-off value of 35 g [116, 117]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [118].

4.13.3 Non-invasive pressure-flow testing

The penile cuff method, in which flow is interrupted to estimate isovolumetric bladder pressure, shows promising data, with good test repeatability [119] and interobserver agreement [120]. A nomogram has also been derived [121] whilst a method in which flow is not interrupted is also under investigation [122].

The data generated with the external condom method [123] correlates with invasive PFS in a high proportion of patients [124]. Resistive index [125] and prostatic urethral angle [126] have also been proposed, but are still experimental.

4.13.4 The diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS compared with pressure-flow studies

The diagnostic performance of non-invasive tests in diagnosing BOO in men with LUTS compared with PFS has been investigated in a SR [127]. A total of 42 studies were included is this review. The majority were prospective cohort studies, and the diagnostic accuracy of the following non-invasive tests were assessed: penile cuff test; uroflowmetry; DWT/BWT; bladder weight; external condom catheter method; IPP; Doppler US; prostate volume/height; and near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the different urodynamic definitions of BOO used across different studies and the small number of studies for each test. It was found that specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable. Therefore, even though several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive urodynamics remains the modality of choice.

Summary of evidence	**LE**
Data regarding the diagnostic accuracy of non-invasive tests is limited by the heterogeneity of the studies as well as the small number of studies for each test.	1a
Specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable.	1a

Recommendation	**Strength rating**
Do not offer non-invasive tests as an alternative to pressure-flow studies for diagnosing bladder outlet obstruction in men.	Strong

4.14 Novel assessment

4.14.1 Visual prostate symptom score

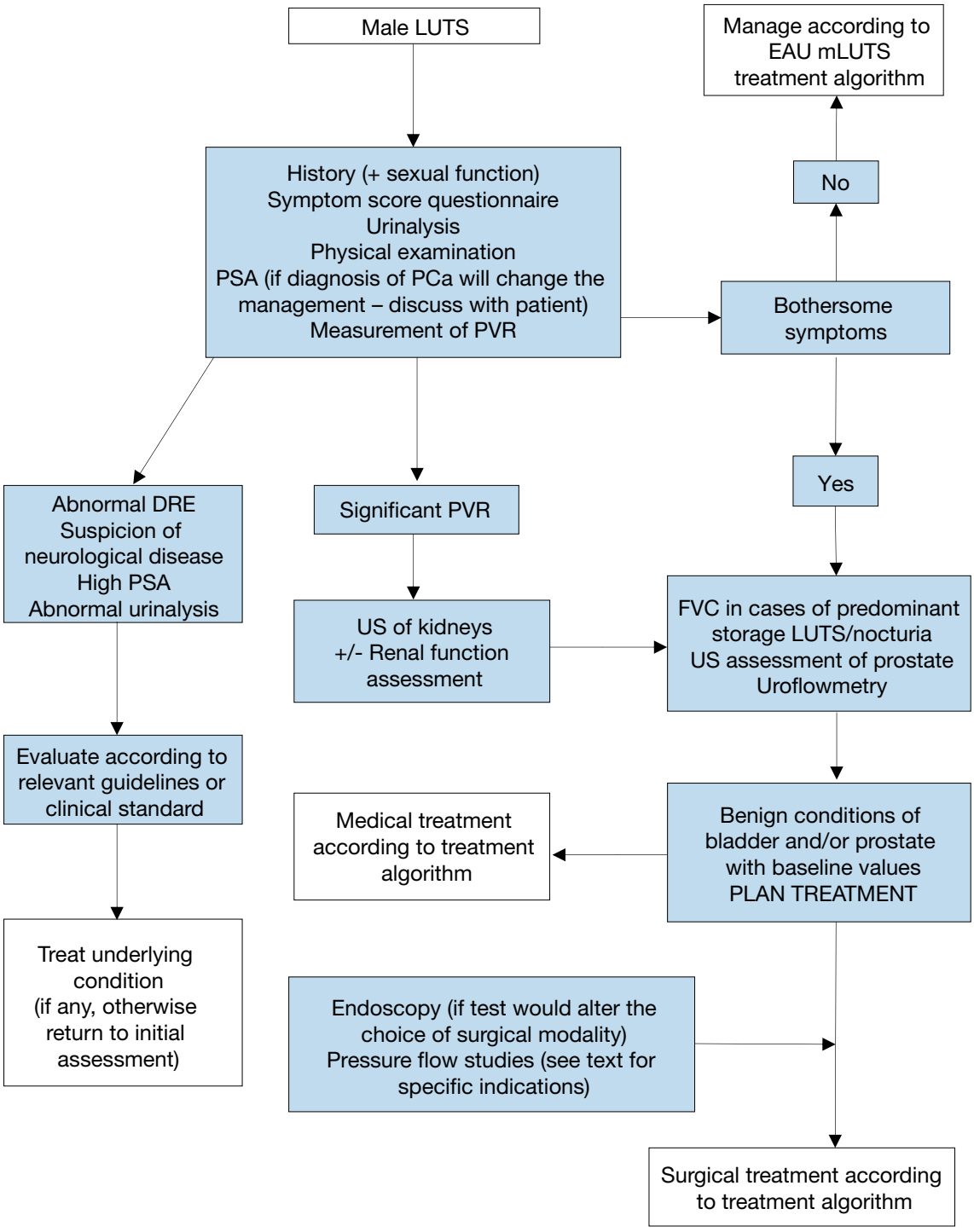
A novel visual prostate symptom score (VPSS) has been prospectively tested vs. the IPSS and correlated positively with the IPSS score [128, 129]. This visual score can be used as an option in men with limited literacy.

4.14.2 Micro-RNA

The use of miR-221 has been shown to have the potential to be used as a biomarker and novel target in the early diagnosis and therapy of BPH [130].

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older

Readers are strongly recommended to read the full text that highlights the current position of each test in detail.


Male LUTS
History (+ sexual function)
Symptom score questionnaire
Urinalysis
Physical examination
PSA (if diagnosis of PCa will change the management – discuss with patient)
Measurement of PVR
Manage according to EAU mLUTS treatment algorithm
No
Bothersome symptoms
Yes
Abnormal DRE
Suspicion of neurological disease
High PSA
Abnormal urinalysis
Significant PVR
US of kidneys
+/- Renal function assessment
FVC in cases of predominant storage LUTS/nocturia
US assessment of prostate
Uroflowmetry
Evaluate according to relevant guidelines or clinical standard
Medical treatment according to treatment algorithm
Benign conditions of bladder and/or prostate with baseline values
PLAN TREATMENT
Treat underlying condition
(if any, otherwise return to initial assessment)
Endoscopy (if test would alter the choice of surgical modality)
Pressure flow studies (see text for specific indications)
Surgical treatment according to treatment algorithm

DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

5. DISEASE MANAGEMENT

5.1 Conservative treatment

5.1.1 Watchful waiting

Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish symptom severity and to differentiate between men with uncomplicated (the majority) and complicated LUTS. Watchful waiting is a viable option for many men with non-bothersome LUTS as few will progress to AUR and complications (e.g. renal insufficiency or stones) [131, 132], whilst others can remain stable for years [133]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [134].

A study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed the surgical group had improved bladder function (flow rates and PVR volumes), especially in those with high levels of bother; 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group [135, 136]. Increasing symptom bother and PVR volumes are the strongest predictors of WW failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

5.1.2 Behavioural and dietary modifications

It is customary for this type of management to include the following components:

- education (about the patient's condition);
- reassurance (that cancer is not a cause of the urinary symptoms);
- periodic monitoring;
- lifestyle advice [133, 134, 137, 138] such as:
    - reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g., at night or when going out in public);
    - avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia;
    - use of relaxed and double-voiding techniques;
    - urethral milking to prevent post-micturition dribble;
    - distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control OAB symptoms;
    - bladder retraining that encourages men to hold on when they have urgency to increase their bladder capacity and the time between voids;
    - reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics);
    - providing necessary assistance when there is impairment of dexterity, mobility, or mental state;
    - treatment of constipation.

Evidence exists that self-management as part of WW reduces both symptoms and progression [137, 138]. Men randomised to three self-care management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only, for up to a year [137]. A SR and meta-analysis found reasonable certainty in estimates that self-management intervention significantly reduced symptom severity in terms of IPSS at six months compared with usual care [139]. The reduction in IPSS score with self-management was similar to that achieved with drug therapy at six to twelve weeks. Self-management had a smaller, additional benefit at six weeks when added to drug therapy [139].

5.1.3 Practical considerations

The components of self-care management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [140]. Further research in this area is required.

Summary of evidence	LE
Watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay treatment. The treatment failure rate over a period of five years was 21%; 79% of patients were clinically stable.	1b
An additional study reported 81% of patients were clinically stable on WW after a mean follow-up of seventeen months.	2

Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care alone at up to a year. Self-care management as part of WW reduces both symptoms and progression.	1b
Self-management achieved a clinically meaningful reduction in symptom severity at six months compared to usual care. There was also a small but significant additional benefit of adding self-management to drug therapy.	1b

Recommendations	Strength rating
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	Strong
Offer men with LUTS lifestyle advice and self-care information prior to, or concurrent with, treatment.	Strong

5.2 Pharmacological treatment

5.2.1 α1-Adrenoceptor antagonists (α1-blockers)

Mechanism of action: α1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [141]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [142], and treatment-associated improvement of LUTS correlates poorly with obstruction [143]. Thus, other mechanisms of action may also be relevant.

Alpha 1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α1-adrenoceptor subtypes (α1B- or α1D-adrenoceptors) may play a role as mediators of effects. Alpha 1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

Currently available α1-blockers are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin); and naftopidil. Alpha 1-blockers exist in different formulations. Although different formulations result in different pharmacokinetic and tolerability profiles, the overall difference in clinical efficacy between the difference formulations seems negligible.

Efficacy: Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [144]. Clinical effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [143].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25%. However, substantial improvements also occurred in the corresponding placebo arms [63, 145]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [63, 145]. A recent SR and meta-analysis suggested that Q_{max} variation underestimates the real effect of α1-blockers on BPO, as small improvements in Q_{max} correspond to relevant improvements in BOO index in PFS [146].

Alpha 1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [65, 147-150]. The efficacy of α1-blockers is similar across age groups [145]. A pooled analysis of phase III and IV trials of silodosin 8 mg demonstrated that improvements in total, storage, voiding, and QoL IPSS scores were similar for the severe and not severe LUTS cohorts [151]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [148-150]; however, recent evidence suggests that the use of α1-blockers (alfuzosin and tamsulosin) may improve resolution of AUR [152]. Nonetheless, IPSS reduction and Q_{max} improvement during α1-blocker treatment appears to be maintained over at least four years.

Tolerability and safety: Tissue distribution, subtype selectivity, and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin and are less common with alfuzosin and tamsulosin [153]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [154]. In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo [155]. In a large retrospective cohort analysis of men aged > 66 years treated with α1-blockers the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR 1.16) was increased, most likely as a result of induced hypotension [156].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [157]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [158]. However, the OR for IFIS was much higher for

tamsulosin. It appears prudent not to initiate α1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α1-blocker use.

A SR concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but can cause abnormal ejaculation [159]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. In a recent meta-analysis ejaculatory dysfunction (EjD) was significantly more common with α1-blockers than with placebo (OR: 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR: 0.80 and 1.78) were associated with a low risk of EjD [160]. In the meta-regression, the occurrence of EjD was independently associated with the improvement of urinary symptoms and flow rate, suggesting that the more effective the α1-blocker is the greater the incidence of EjD.

Practical considerations: α1-blockers are usually considered the first-line drug treatment for male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. However, α1-blockers do not prevent occurrence of urinary retention or need for surgery. Ophthalmologists should be informed about α1-blocker use prior to cataract surgery. Elderly patients treated with non-selective α1-blockers should be informed about the risk of orthostatic hypotension. Sexually active patients treated with selective α1-blockers should be counselled about the risk of EjD.

Summary of evidence	**LE**
Alpha 1-blockers are effective in reducing urinary symptoms (IPSS) and increasing the peak urinary flow rate (Q_{max}) compared with placebo.	1a
Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo.	1a
Alfuzosin, doxazosin, tamsulosin or terazosin exposure has been associated with an increased risk of IFIS.	1a
Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin.	1a

Recommendation	**Strength rating**
Offer α1-blockers to men with moderate-to-severe LUTS.	Strong

*5.2.2 **5α-reductase inhibitors***

Mechanism of action: Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5α-reductase [161], which has two isoforms:

- 5α-reductase type 1: predominant expression and activity in the skin and liver.
- 5α-reductase type 2: predominant expression and activity in the prostate.

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits both 5α-reductase types (dual 5-ARI). The 5-ARIs induce apoptosis of prostate epithelial cells [162] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after six to twelve months of treatment [163]. Mean prostate volume and PSA reduction may be even more pronounced after long-term treatment. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5-ARIs.

Efficacy: Clinical effects relative to placebo are seen after treatment of at least six months. After two to four years of treatment 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement [65, 149, 150, 164-170]. An indirect comparison and one direct comparative trial (twelve months duration) indicated that dutasteride and finasteride are equally effective in the treatment of LUTS [163, 171]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [172]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of AUR, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40 mL [173, 174]. A long-term trial with dutasteride in symptomatic men with prostate volumes > 30 mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as the α1-blocker tamsulosin [149, 170, 175]. The greater the baseline prostate volume (or serum PSA level), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5α-reductase inhibitors, but not α1-blockers, reduce the long-term (> 1 year) risk of AUR or need for surgery [65, 168, 176]. In the PLESS study, finasteride reduced the relative risk of AUR by 57% and need for surgery by 55% (absolute risk reduction 4% and 7%, respectively) at four years, compared with placebo [168]. In the MTOPS study, finasteride reduced the relative risk of AUR by 68% and need for surgery by 64% (absolute risk reduction 2% and 3%, respectively), also at four years [65]. A pooled analysis of three RCTs with two-year follow-up data, reported that treatment with finasteride decreased the relative risk of AUR by 57%, and surgical intervention by 34% (absolute risk reduction 2% for both) in patients with moderately symptomatic LUTS [177]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPO-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [178, 179]. Furthermore, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [180, 181].

Tolerability and safety: The most common adverse events are reduced libido, erectile dysfunction (ED) and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [65, 150, 163, 182]. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients. Two studies have suggested that treatment with 5-ARIs is associated with a higher incidence of high-grade cancers although no causal relationship has been proven [183, 184]. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [185]. Population-based studies in Taiwan and Ontario did not find an association between the use of 5-ARIs and increased cardiovascular side effects [185, 186]. In a British-Taiwanese population-based cohort study, the risk of type II diabetes was higher in men with 5-ARIs than in men receiving tamsulosin but did not differ between dutasteride and finasteride [187].

Practical considerations: Treatment with 5-ARIs should be considered in men with moderate-to-severe LUTS and an enlarged prostate (> 40 mL) and/or elevated PSA concentration (> 1.4-1.6 ng/mL). They can prevent the risk of AUR and need for surgery. Due to the slow onset of action, they are not suitable for short-term use. Their effect on PSA needs to be considered in relation to PCa screening.

Summary of evidence	**LE**
After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement.	1b
5α-reductase inhibitors can prevent disease progression with regard to AUR and the need for surgery. Due to 5-ARIs slow onset of action, they are suitable only for long-term treatment (years).	1a
The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, ED and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume.	1b

Recommendations	**Strength rating**
Use 5α-reductase inhibitors (5-ARIs) in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL).	Strong
Counsel patients about the slow onset of action of 5-ARIs.	Strong

*5.2.3 **Muscarinic receptor antagonists***

Mechanism of action: The detrusor is innervated by parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells. Muscarinic receptors are also present on other cell types, such as bladder urothelial cells and epithelial cells of the salivary glands. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. The M2 subtype is more numerous, but the M3 subtype is functionally more important in bladder contractions [188, 189]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [190, 191].

The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); and trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [192, 193].

Efficacy: Antimuscarinics were mainly tested in females in the past, as it was believed that LUTS in men were caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for this assumption [194]. A sub-analysis of an open-label trial of OAB patients showed that age, but

not gender had an impact on urgency, frequency, or urgency incontinence [195]. In a pooled analysis, which included a sub-analysis of male patients, fesoterodine 8 mg was superior to tolterodine extended release (ER) 4 mg for the improvement of severe urgency episodes/24 hours and the OAB-q Symptom Bother score at week twelve, the urinary retention rate was around 2% [196].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested [197-202]. Most trials lasted only twelve weeks. Four *post hoc* analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [194, 198, 203]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit [204]. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores, and overall perception of bladder problems. Fesoterodine improved micturition frequency, urgency episodes, and UUI episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after twelve to 25 weeks [199, 202]. The TIMES RCT reported that tolterodine ER monotherapy significantly improved UUI episodes per 24 hours compared to placebo, at week twelve. Tolterodine ER did not significantly improve urgency, IPSS total or QoL score compared with placebo [201].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinics [205]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [202, 206]. In a small RCT propiverine improved frequency and urgency episodes [206].

Tolerability and safety: Antimuscarinic drug trials generally show approximately 3-10% withdrawals, which is similar to placebo. Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8 mg showed higher PVRs (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [199]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8 mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4 mg (both 0.8%). These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Theoretically antimuscarinics might decrease bladder strength, and hence might be associated with PVR or urinary retention. A twelve week safety study on men with mild-to-moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not AUR (3% in both arms) [207]. The urodynamic effects included larger bladder volumes at first detrusor contraction, higher maximum cystometric capacity, and decreased bladder contractility index, Q_{max} was unchanged. This trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [194].

Practical considerations: Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of muscarinic receptor antagonists in men of any age with LUTS are not yet available. In addition, only patients with low PVR volumes at baseline were included in the studies. These drugs should therefore be prescribed with caution, and regular re-evaluation of IPSS and PVR is advised. Men should be advised to discontinue medication if worsening voiding LUTS or urinary stream is noted after initiation of therapy.

Summary of evidence	**LE**
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	2
Antimuscarinic monotherapy can be associated with increased PVR after therapy, but acute retention is a rare event in men with a PVR volume of < 150 mL at baseline.	2

Recommendations	**Strength rating**
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Strong
Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL.	Weak

*5.2.4 **Beta-3 agonist***

Mechanism of action: Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. The mode of action of beta-3 agonists is not fully elucidated [208].

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist with approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in RCTs conducted in Europe, Australia, North America and Japan [209-213]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency and UUI and also patient perception of treatment benefit. These studies had a predominantly female study population. A meta-analysis of eight RCTs including 10,248 patients (27% male) found that mirabegron treatment resulted in reduced frequency, urgency and UUI rates, as well as an improved voided volume with a statistically significant improvement of nocturia compared with both placebo and tolterodine [214].

Mirabegron has been evaluated in male patients with OAB in the context of LUTS either associated or not associated with BPO confirmed by urodynamics [215]. Mirabegron 25 mg daily led to increased satisfaction and improved QoL, but symptoms assessed by validated questionnaires (IPSS and OAB-SS), only improved in non-obstructed patients. Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [216], again in a predominantly female study population. An Asian study with a higher proportion of male subjects (approximately one third) reported superiority over placebo in reducing frequency of micturition, but did not report the results separately for the genders [217].

In a study of more than 1,000 patients of whom approximately 30% were male, combination therapy of mirabegron 25/50 mg and solifenacin 5/10 mg was associated with statistically significant improvements in patient outcomes and health related QoL vs. solifenacin 5 mg and placebo; however, they did not separate out the effects in men and women [218]. In another study, in which 28% patients were male, mirabegron significantly improved patient reported perception of their condition and QoL whether or not patients were incontinent [219]. A phase IV study, with a small proportion of male subjects, reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [220].

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [209-212]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg, or both). Blood pressure should be measured before starting treatment and monitored regularly during treatment. A combination of thirteen clinical studies including 13,396 patients, 25% of whom were male, showed that OAB treatments (anticholinergics or mirabegron) were not associated with an increased risk of hypertension or cardiovascular events compared to placebo [221]. The proportion of patients with dry mouth and constipation in the mirabegron groups was notably lower than reported in RCTs of other OAB agents or of the active control tolterodine [209]. Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron did not adversely affect voiding urodynamic parameters compared to placebo in terms of Q_{max}, detrusor pressure at maximum flow and bladder contractility index [222]. The overall change in PVR with mirabegron is small [222].

A small prospective study (mainly focused on males) has shown that mirabegron 25 mg is safe in patients aged 80 years or more with multiple comorbidities [223]. A pooled analysis of three trials, each of twelve weeks and a one-year trial showed, in patients aged > 65 years, a more favourable tolerability profile for mirabegron than antimuscarinics [224]. The PILLAR phase IV study also showed that in a large population of 888 patients ≥ 65 years (approx. 30% of males), mirabegron 50 mg was safe and effective [225]. In an eighteen-week study of 3,527 patients (23% male), the incidence of adverse events was higher in the combination (solifenacin 5 mg plus mirabegron 25 mg) group (40%) than the mirabegron 25 mg alone group (32%). Events recorded as urinary retention were low (< 1%) but were reported slightly more frequently in the combined group when compared with the monotherapy and placebo groups. The PVR volume was slightly increased in the combined group compared with solifenacin 5 mg, and the mirabegron monotherapy and placebo groups. Combined therapy with solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg provided improvements in efficacy generally consistent with an additive effect [226].

In a retrospective analysis of persistence and adherence in 21,996 patients, of whom 30% were male, the median time to discontinuation was significantly longer for mirabegron (169 days) compared to tolterodine (56 days) and other antimuscarinics (30-78 days). There was no statistical difference between men and women [227].

The phase III EMPOWUR trial comparing vibegron to placebo and tolterodine showed once daily 75 mg vibegron provided statistically significant reductions in micturitions, urgency episodes and UUI [228]. Treatment was well tolerated with a favourable safety profile. However, the majority of the study population (85%) were female and vibegron is not yet licenced in Europe.

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Available studies on mirabegron in combination with antimuscarinics in OAB patients had a predominantly female study population, while further trials are still pending.

Summary of evidence	LE
Mirabegron improves storage LUTS, including urinary frequency, urgency and UUI.	2
Patients prescribed mirabegron remained on treatment longer than those prescribed antimuscarinics.	3

Recommendation	Strength rating
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Weak

*5.2.5 **Phosphodiesterase 5 inhibitors***

Mechanism of action: Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDE5Is might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [229]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [230]. Phosphodiesterase 5 inhibitors could also reduce chronic inflammation in the prostate and bladder [231]. The exact mechanism of PDE5Is on LUTS remains unclear.

Although clinical trials of several selective oral PDE5Is have been conducted in men with LUTS, only tadalafil 5 mg once daily has been licensed for the treatment of male LUTS.

Efficacy: Randomised controlled trials have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL. However, Q_{max} did not significantly differ from placebo in most trials [232]. A Cochrane review included a total of sixteen RCTs that examined the effects of PDE5Is compared to placebo and other standard of care drugs (α1-blockers and 5-ARIs) in men with LUTS [233]. In the updated meta-analysis, PDE5Is led to a small reduction (mean difference (MD) 1.89 lower; 95% CI: 2.27 lower to 1.50 lower; n = 4293) in IPSS compared to placebo [233]. There was no difference between PDE5Is and α1-blockers in IPSS [234]. Most evidence was limited to short-term treatment up to twelve weeks. In other meta-analyses, PDE5Is were also found to improve IPSS and IIEF score, but not Q_{max} [235, 236]. A meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [235].

In a *post hoc* analysis of data pooled from four blinded trials of tadalafil 5 mg vs. placebo once daily, a minimum improvement of 25% in IPSS score was found in 60% in the tadalafil group vs. 44% in the placebo group [237]. The maximum trial duration was 52 weeks [238]. A subgroup analysis of pooled data from four RCTs demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of α-blockers or PDE5Is, total testosterone level or predicted prostate volume [239]. In a *post hoc* analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/ comorbidities, except for patients receiving more than one antihypertensive medication. Among sexually active men > 45 years, tadalafil improved both LUTS/BPH and ED [239].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%) vs. indirect (7.5%) treatment effects via IIEF-EF improvement [240]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [241]. An integrated analysis of RCTs showed that tadalfil was not superior to placebo for IPSS improvement at twelve weeks in men ≥ 75 years (with varied effect size between studies), but was for men < 75 years [242]. An open label urodynamic study of 71 patients showed significant improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3 to 47.1), and resolution of DO in fifteen (38%) of 38 patients. Significant flow rate improved from 7.1 to 9.1 mL/s and mean IPSS from 18.2 to 13.4 [249].

A multicenter, double blind, placebo controlled RCT compared once daily tadalafil 20 mg vs. placebo during twelve weeks in men with LUTS with or without BOO. Urodynamic measures including detrusor pressure at maximum urinary flow rate, Q_{max}, maximum detrusor pressure, BOO or bladder capacity remained largely unchanged during the study with no statistically significant or clinically adverse event differences between tadalafil and placebo [243].

A combination of PDE5Is and α-blockers has also been evaluated. A meta-analysis of five RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q_{max} (+1.5 mL/s) compared with α-blockers alone [235]. Both a SR and Cochrane review found similar findings [233, 244]. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a 26-week placebo-controlled RCT. The combination of tadalafil and finasteride provided a significant early improvement in urinary symptoms at four, twelve and 26 weeks as well as a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [245]. However, only tadalafil 5 mg has been licensed in the context of LUTS management while data on combinations of PDE5Is and other LUTS medications is emerging.

Tolerability and safety: Reported adverse effects in RCTs comparing the effect of all PDE5Is vs. placebo in men with LUTS include flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [235].

Tadalafil is contraindicated in patients using nitrates or guanylate cyclase stimulators, such as riociguat, and in men with cardiac disease for whom sexual activity is inadvisable [246]. Tadalafil is also contraindicated in patients with myocardial infarction within the last 90 days, - patients with unstable angina or angina occurring during sexual intercourse, - patients with New York Heart Association Class 2 or greater heart failure in the last six months, - patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension, - patients with a stroke within the last six months or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is [246]. Detailed information regarding tolerability/safety of all available PDE5Is for the treatment of ED in men treated with α-blockers for LUTS are provided by the EAU Guidelines on Sexual and Reproductive Health [247].

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without ED. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one-year follow-up [238]; limiting conclusions about efficacy or tolerability greater than one year. There is limited information on reduction of prostate size and no data on disease progression.

Summary of evidence	LE
Phosphodiesterase 5 inhibitors significantly improve IPSS and IIEF score, but not Q_{max}.	1a

Recommendation	Strength rating
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	Strong

*5.2.6 **Plant extracts - phytotherapy***

Potential mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits. There are single plant preparations (mono-preparations) and preparations combining two or more plants in one pill (combination preparations) [248].

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [248]. *In vitro*, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [248-250]. The *in vivo* effects of these compounds are uncertain, and the precise mechanisms of plant extracts remain unclear.

Efficacy: The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects; therefore, the effects of one brand cannot be extrapolated to others [251]. In addition, batches from the same producer may contain different concentrations of active ingredients [252]. A review of recent extraction techniques and their impact on the composition/biological activity of available *Serenoa repens* based products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds [253], as the pharmacokinetic properties of the different preparations can vary significantly.

Heterogeneity and a limited regulatory framework characterise the current status of phytotherapeutic agents. The European Medicines Agency (EMA) has developed the Committee on Herbal Medicinal Products (HMPC). European Union (EU) herbal monographs contain the HMPC's scientific opinion on safety and efficacy data about herbal substances and their preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, whilst also documenting long-standing use and experience in the EU. European Union monographs are divided into two sections: a) Well established use (marketing authorisation): when an active ingredient of a medicine has been used for more than ten years and its efficacy and safety have been well established (including a review of the relevant literature); and b) Traditional use (simplified registration): for herbal medicinal products which do not fulfil the requirements for a marketing authorisation, but there is sufficient safety data and plausible efficacy on the basis of long-standing use and experience.

The HPMC periodically invites all interested parties to submit any scientific data that the Committee should consider during their periodic review of the monographs. Table 1 lists the available EU monographs for herbal medicinal products and the current calls for update.

Table 1: European Union monographs for herbal medicinal products [254]

Herbal substance	HMPC evaluation	Therapeutic Indication by HMPC	Date of monograph
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: hexane [255]	Well established use	Symptomatic treatment of BPH	14/01/2016 Addendum 1/9/21**
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: ethanol [255]	Traditional use	LUTS related to BPH*	14/01/2016 Addendum 1/9/21**
Cucurbita pepo L, semen (pumpkin seed) Preparation as defined in the monograph [256]	Traditional use	LUTS related to BPH or related to an OAB*	25/03/2013 Call ended 30/4/21
Prunus africana (Hook f.) Kalkm., cortex (pygeum africanum bark) Preparation as defined in the monograph [257]	Traditional use	LUTS related to BPH*	01/09/2017 No call for update
Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix Preparation as defined in the monograph [258]	Traditional use	LUTS related to BPH*	05/11/2012 Call ended 30/6/21
Epilobium angustifolium L. and/or *Epilobium parviflorum Schreb., herba (Willow herb)* Preparation as defined in the monograph [259]	Traditional use	LUTS related to BPH*	13/01/2016 No call for update

** After serious conditions have been excluded by a medical doctor.*

*** Addendum concluded that no revision was needed.*

Panel interpretation: Only hexane extracted *Serenoa repens* (HESr) has been recommended for well-established use by the HMPC. Based on this a detailed scoping search covering the timeframe between the search cut-off date of the EU monograph and May 2021 was conducted for HESr.

A large meta-analysis of 30 RCTs with 5,222 men and follow-up ranging from four to 60 weeks, demonstrated no benefit of treatment with *S. repens* in comparison to placebo for the relief of LUTS [260]. It was concluded that *S. repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q_{max}, or prostate size reduction; however, the similar improvement in IPSS or Q_{max} compared with finasteride or tamsulosin could be interpreted as treatment equivalence. Importantly, in the meta-analysis all different brands of *S. repens* were included regardless or not of the presence of HESr as the main ingredient in the extract.

Another SR focused on data from twelve RCTs on the efficacy and safety of HESr [261]. It was concluded that HESr was superior to placebo in terms of improvement of nocturia and Q_{max} in patients with enlarged prostates. Improvement in LUTS was similar to tamsulosin and short-term use of finasteride. An updated SR analysed fifteen RCTs and also included twelve observational studies. It confirmed the results of the previous SR on the efficacy of HESr [262]. Compared with placebo, HESr was associated with 0.64 (95% CI: 0.98 - 0.31) fewer voids/night and an additional mean increase in Q_{max} of 2.75 mL/s (95% CI: 0.57 - 4.93), both were significant. When compared with α-blockers, HESr showed similar improvements in IPSS (WMD 0.57, 95% CI: 0.27 - 1.42) and a comparable increase in Q_{max} when compared to tamsulosin (WMD 0.02; 95% CI: 0.71 - 0.66). Efficacy assessed using IPSS was similar after six months of treatment between HESr and 5-ARIs. Analysis of all available published data for HESr showed a mean significant improvement in IPSS from baseline of 5.73 points (95% CI: 6.91 - 4.54) [262].

A network meta-analysis tried to compare the clinical efficacy of *S. repens* (HESr and non-HESr) against placebo and α1-blockers in men with LUTS. Interestingly, only two RCTs on HESr were included in the analysis. It was found that *S. repens* achieved no clinically meaningful improvement against placebo or α1-blockers in short-term follow-up. However, *S. repens* showed a clinical benefit after a prolonged period of treatment, and HESr demonstrated a greater improvement than non-HESr in terms of IPSS [263].

With respect to safety and tolerability data from the SRs showed that HESr had a favourable safety profile with gastrointestinal disorders being the most frequent adverse effects (mean incidence 3.8%) while HESr had very limited impact on sexual function.

A cross-sectional study compared the combination of HESr with silodosin to silodosin monotherapy in patients treated for at least twelve months (mean duration 13.5 months) [264]. It was reported that 69.9% of the combination therapy patients achieved the predefined clinically meaningful improvement (improvement more than three points in baseline IPSS) compared to 30.1% of patients treated only with silodosin. In addition, a greater than 25% improvement in IPSS was found in 68.8% and 31.2% of the patients in the combination and the monotherapy groups, respectively. These data suggest that combination of a α1-blocker with HESr may result in greater clinically meaningful improvements in LUTS compared to α1-blocker monotherapy [264].

Practical considerations: Available RCTs do not use the same endpoints (e.g. IPSS). More studies on the use of HESr in combination with other pharmacotherapeutic agents for male LUTS are pending. There is a need to define the subpopulation of patients who will benefit most from therapy with HESr.

Summary of evidence	**LE**
Hexane extracted Serenoa repens improves Q_{max} and results in fewer voids/night [0.64 (95% CI: 0.98 to 0.31)] compared to placebo.	2
Hexane extracted Serenoa repens has a very limited negative impact on sexual function.	2

Recommendations	**Strength rating**
Offer hexane extracted *Serenoa repens* to men with LUTS who want to avoid any potential adverse events especially related to sexual function.	Weak
Inform the patient that the magnitude of efficacy of HESr may be modest.	Strong

*5.2.7 **Combination therapies***

5.2.7.1 α1-blockers + 5α-reductase inhibitors

Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a 5-ARI (Section 5.2.2). The α1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop full clinical efficacy. Finasteride has been tested in clinical trials with alfuzosin, terazosin, doxazosin or terazosin, and dutasteride with tamsulosin.

Efficacy: Several studies have investigated the efficacy of combination therapy against an α1-blocker, 5-ARI or placebo alone. Initial studies with follow-up periods of six to twelve months demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas combination therapy of both agents was not superior to α1-blocker monotherapy [165, 166, 265]. In studies with a placebo arm, the α1-blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study showed similar results [65].

Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery [65, 149, 150].

The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α1-blocker for AUR and the need for surgery after eight months [150]. Thus, the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after six to nine months of combination therapy was investigated in an RCT and an open-label multicentre trial [266, 267]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [266], with almost three quarters of patients reporting no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A more recent trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [267]. Lower urinary tract symptom improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.4). The limitations of the studies include the short duration of the studies and the short follow-up period after discontinuation.

In both the MTOPS and CombAT studies, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, incontinence, or an increase in creatinine > 50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy vs. placebo and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [65]. In addition, finasteride (alone or in combination), but not doxazosin alone, significantly reduced both the risks of AUR and the need

for BPO-related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPO-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [268]. To prevent one case of urinary retention and/or surgical treatment thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%.

The CONDUCT study compared efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two-year RCT with a total of 742 patients. In both arms detailed lifestyle advice was given. This fixed-dose combination resulted in a rapid and sustained improvement in men with moderate LUTS at risk of disease progression, the difference in IPSS at 24 months was 5.4 in the active arm and 3.6 in the placebo arm [269]. Furthermore, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as a worsening in symptoms) by 43.1% when compared with WW, with an absolute risk reduction of 11.3% (number needed to treat [NNT] = 9).

The influence of baseline variables on changes in IPSS after combination therapy with dutasteride plus tamsulosin or either monotherapy was tested based on the four-year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [270].

A combination of the 5-ARI finasteride and tadalafil 5 mg was tested in a large scale RCT against finasteride monotherapy. This study supports the concept of this novel combination therapy and is described in more detail in section 5.2.5 [245].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [65, 149, 150]. The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy. The MTOPS study demonstrated that the incidence of treatment related adverse events is higher during the first year of combined treatment between doxazosin and finasteride [271]. A meta-analysis measuring the impact of medical treatments for LUTS/BPH on ejaculatory function, reported that combination therapy with α1-blockers and 5-ARIs resulted in a three-fold increased risk of EjD compared with each monotherapy [160].

Practical considerations: Compared with α1-blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max} and is superior in prevention of disease progression. However, combination therapy is also associated with a higher rate of adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS who are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max}, etc.). Combination therapy should only be used when long-term treatment (more than twelve months) is intended, and patients should be informed of this. Discontinuation of the α1-blocker after six months might be considered in men with moderate LUTS.

Summary of evidence	**LE**
Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery.	1b
The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy vs. placebo and to a greater extent than with either finasteride or doxazosin monotherapy.	1b
The CombAT study found that combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and 5-ARIs.	1b

Recommendation	**Strength rating**
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong

5.2.7.2 α1-blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α1-blocker together with an antimuscarinic aiming to antagonise both α1-adrenoceptors and muscarinic receptors. The possible combinations have not all been tested in clinical trials to date.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting four to twelve weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α1-blocker [193, 204, 268, 272-279]. Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [204, 279]. A SR showed that combination therapy of tolterodine and an α1-blocker was significantly more efficacious than either monotherapy for 24-hours and night voiding frequency, and 24-hours urgency episodes [204].

One trial used the α1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [280]. A high proportion of men with voiding and storage LUTS need to add anticholinergics after α1-blocker monotherapy, particularly those with longer duration of symptoms at presentation, and men with storage symptoms and a small prostate volume [281].

Symptom improvement is higher regardless of PSA concentration with combination therapy, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [205].

Persistent LUTS during α1-blocker treatment can be reduced by the additional use of an antimuscarinic, [268, 272, 278, 282, 283]. Two SRs of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [284, 285]. In a meta-analysis of sixteen studies with 3,548 patients with BPH/OAB, initial combination treatment of an α1-blocker with anticholinergic medication improvement storage symptoms and QoL compared to α1-blocker monotherapy without causing significant deterioration of voiding function [286]. There was no difference in total IPSS and Q_{max} between the two groups.

Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [287]. Long term use of combination therapy has been reported in patients receiving treatment for up to one year, showing symptomatic response is maintained, with a low incidence of AUR [288]. In men with moderate-to-severe storage symptoms, voiding symptoms and PVR < 150 mL, the reduction in symptoms using combination therapy is associated with patient-relevant improvements in health related QoL compared with placebo and α1-blocker monotherapy [289].

The intake of fixed-dose combination tablet containing solifenacin 6 mg and tamsulosin 0.4 mg improved OAB-q symptom bother in > 80% of LUTS/BPH patients not adequately responding to monotherapy, with a high treatment persistence (77% at weeks 40 to 52), and a low risk of AUR [290]. Combined behavioural and drug therapy yielded greater improvements in OAB symptoms than drug therapy alone, but not behavioural therapy alone, in a RCT evaluating the effectiveness of combined behavioural strategies and drug therapy for OAB symptoms in men [291].

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics. The most common side-effect is dry mouth. Some side-effects (e.g. dry mouth or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low up to one year of treatment [201, 284, 292]. Antimuscarinics do not cause evident deterioration in Q_{max} used in conjunction with an α1-blocker in men with OAB symptoms [279, 293].

A recent RCT investigated safety in terms of maximum detrusor pressure and Q_{max} for solifenacin (6 mg or 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo [294]. The combination therapy was non-inferior to placebo for the primary urodynamic variables; Q_{max} was increased vs. placebo [294].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α1-blocker and antimuscarinic. Trials used mainly storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR is recommended during combination treatment.

Summary of evidence	**LE**
Combination treatment with α1-blockers and antimuscarinics is effective for improving LUTS-related QoL impairment.	2
Combination treatment with α1-blockers and antimuscarinics is more effective for reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone.	2
Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics.	1
There is a low risk of AUR using α1-blockers and antimuscarinics in men known to have a PVR urine volume of < 150 mL.	2

Recommendations	Strength rating
Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	Strong
Do not prescribe combination treatment in men with a post-void residual volume > 150 mL.	Weak

5.2.7.3 α1-blockers + Beta-3 agonist

Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a beta-3 agonist (Section 5.2.4) as an add-on therapy in males receiving α1-blockers with persisting OAB symptoms.

Efficacy: The MATCH study explored the effect of the addition of mirabegron 50 mg to tamsulosin 0.2 mg compared to tamsulosin plus placebo in 544 patients [295]. A statistically significant difference of 0.52 voids per day was seen in favour of mirabegron. Total IPSS score also improved, but was not significant between the groups. Another RCT evaluated add-on therapy with mirabegron for OAB symptoms persisting after treatment with tamsulosin 0.2 mg daily in men with BPO [296]. Combination therapy was associated with greater improvements in OAB symptom score, in urinary urgency and daytime frequency as well as the storage sub-score of IPSS and QoL index compared to monotherapy with tamsulosin [297].

The PLUS phase IV trial [296] compared mirabegron and placebo in a population of males treated with a standard dose of tamsulosin 0.4 mg. After a four-week run-in period of treatment with tamsulosin 0.4 mg alone, 715 patients were randomised between placebo and mirabegron 25 mg, upgraded to 50 mg after one month. While mean number of micturition's were significantly reduced in the experimental arm, the effect size was deemed as low (mean adjusted difference of 0.39 voids per day). Similar results were seen for mean voided volume and urgency episodes, but total IPSS, IPSS sub-scores and OAB-q symptom score were not significantly different between the groups.

A RCT comparing the efficacy of mirabegron 50 mg or fesoterodine 4 mg add-on therapy to silodosin in LUTS patients with persisting OAB symptoms reported that at three months, fesoterodine add-on therapy showed a significantly greater improvement than mirabegron add-on therapy in OAB symptom score and urgency score and IPSS-QoL score [218]. Fesoterodine was also superior in alleviating DO.

Tolerability and safety: In the MATCH study main adverse events were in line with previous trials, and cardiovascular events were uncommon in the studied populations [295]. The PLUS phase IV trial also reported adverse events similar to those seen in previous trials (hypertension, headache and nasopharyngitis being the most frequent) [296]. There were six episodes of retention recorded (1.7%) and overall, no clinically significant specific change was seen in Q_{max} and PVR. An open-label, randomised, 2-arm, 2-sequence study reported that the addition of mirabegron or tamsulosin to patients under tamsulosin or mirabegron monotherapy did not cause clinically relevant changes in cardiovascular safety or safety profiles [298].

Solifenacin and mirabegron were also compared in another RCT that has shown comparable efficacy but a better safety profile for mirabegron [299].

Practical considerations: Add-on therapy with mirabegron in patients with remaining symptoms under α1-blocker therapy has been evaluated only in short-term clinical trials. The short-term benefit remains uncertain with a low effect size in urinary frequency compared to placebo, and more studies with longer follow-up are required.

Summary of evidence	LE
Combination treatment with α1-blockers and mirabegron results in a slight decrease of number of voids and urgency episodes per day compared with α1-blockers alone.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and mirabegron.	1b

Recommendations	Strength rating
Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy.	Weak

Note: All patients should be counselled about pharmacological treatment related adverse events in order to select the most appropriate treatment for each individual patient.

5.3 Surgical treatment

Surgical treatment is one of the cornerstones of LUTS/BPO management. Based on its ubiquitous availability, as well as its efficacy, M-TURP has long been considered as the reference technique for the surgical management of LUTS/BPO. However, in recent years various techniques have been developed with the aim of providing a safe and effective alternative to M-TURP. Previously, the surgical section of the Guidelines was based on technology rather than surgical approach. As the clinical reality is primarily reflected by surgical approach and not necessarily by a specific technology, the chapter on surgical management has been restructured. It is now divided into the following five sections:

1. Resection;
2. Enucleation;
3. Vaporisation;
4. Alternative ablative techniques; and
5. Non-ablative techniques.

In addition, most of the studies are restricted by prostate size, which is also reflected in the present Guidelines. Notably, only a small fraction of RCTs are performed in patients with a prostate > 80 mL; therefore, high-level evidence for larger prostates are limited.

Based on Panel consensus, timeframes defining short-, mid- and long-term follow-up of patients submitted to surgical treatments are twelve, 36, and over 36 months, respectively. The durability of a technique is reflected by the re-operation rate during follow-up, the failure to wean patients off medication as well as the initiation of novel LUTS medication after surgery. However, for the majority of techniques only the re-operation rate is reported, and clinicians should inform patients that long-term surgical RCTs are often lacking. Some patients value sexual function and perceived higher safety over maximum efficacy and it is not therefore surprising that some patients consciously choose an alternative ablative or non-ablative technique despite the knowledge that it might not be their definitive treatment. In contrast, many urologists are critical about these procedures due to their inferior relief of BOO.

Recommendations on new devices or interventions will only be included in the Guidelines once supported by a minimum level of evidence. To clarify this the Panel have published their position on certainty of evidence (CoE) [300]. In summary, a device or technology is only included once supported by RCTs looking at both efficacy and safety, with adequate follow-up, and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies [300]. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include proof of concept, RCTs on efficacy and safety, as well as cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms [300]. The panel assesses the quality of all RCTs and if they do not meet the standard required the intervention will continue to have no recommendation i.e., a RCT does not guarantee inclusion in the Guidelines.

In addition, the Guidelines continues to include techniques under investigation. These are devices or technologies that have shown promising results in initial studies; however, they do not meet the aforementioned criteria yet to provide a CoE which allows the Panel to regard these devices or technologies as recommended alternatives. To account for evolving evidence, recommendations for some techniques under investigation have been made; however, these techniques remain under investigation until further studies provide the recommended CoE.

*5.3.1 **Resection of the prostate***

5.3.1.1 Monopolar and bipolar transurethral resection of the prostate

Mechanism of action: Transurethral resection of the prostate (TURP) is performed using two techniques: monopolar TURP (M-TURP) and bipolar TURP (B-TURP). Monopolar transurethral resection of the prostate removes tissue from the transition zone of the gland. Bipolar TURP addresses a major limitation of M-TURP by allowing performance in normal saline. Prostatic tissue removal is identical to M-TURP. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ("true" bipolar systems) or the sheath ("quasi" bipolar systems). The various bipolar devices available differ in the way in which current flow is delivered [301, 302].

Efficacy: In a meta-analysis of twenty RCTs with a maximum follow-up of five years, M-TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [303]. Monopolar-TURP delivers durable outcomes as shown by studies with a follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO [304]. One study with a mean follow-up of thirteen years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with DUA rather than re-development of

BPO [102]. A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A SR analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of sixteen months [305]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed that the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) remained unchanged during the last decade (0.9%, 3.7%, 9.5% and 12.7% at three months, one year, five years, and eight years, respectively), and that the respective incidence of re-TURP was 0.8%, 2.4%, 6.1% and 8.3%, respectively [306, 307].

Bipolar TURP is the most widely investigated alternative to M-TURP. Pooled results from 59 RCTs have been reported to date [308]. Early pooled results as well as at twelve months, concluded that no clinically relevant differences exist in short-term efficacy (IPSS, QoL score and Q_{max}) [308, 309]. Subsequent meta-analyses supported these conclusions though trial quality was generally poor [303, 310-313]. The largest meta-analysis published to date, confirmed that B-TURP compared to M-TURP results in little to no difference in urological symptoms and bother (IPSS and QoL score) at twelve months [308]. Data from RCTs with mid- to long-term follow-up (up to 60 months) showed no differences in efficacy parameters [314-322]. A meta-analysis of RCTs comparing B-TURP vs. M-TURP, reported similar efficacy at 36 months in terms of IPSS, and Q_{max} [323].

A meta-analysis was conducted to evaluate the quasi-bipolar transurethral resection in saline (TURis, Olympus Medical) system vs. M-TURP. Ten unique RCTs (1,870 patients) were included, and it was concluded that TURis was of equivalent efficacy to M-TURP [324].

Tolerability and safety: Peri-operative mortality and morbidity of M-TURP have decreased over time, but morbidity remains considerable (0.1% and 11.1%, respectively) [325]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed a 20% reduction in mortality rate over time, to 0.1% at 30 days and 0.5% at 90 days [306, 307].

The risk of TUR-syndrome decreased to < 1.1% [305, 326]. Data from 10,654 M-TURPs reported bleeding requiring transfusion in 2.9% [325]. Short- to mid-term complications reported in an analysis of RCTs using M-TURP as a comparator were: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%), and UTI 4.1% (0-22%) [303]. Long-term complications of M-TURP comprise urinary incontinence (UI), urinary retention and UTIs, bladder neck contracture (BNC), urethral stricture, retrograde ejaculation and ED [305].

Early pooled results concluded that no differences exist in short-term urethral stricture/BNC rates, but B-TURP is preferable to M-TURP due to a more favourable peri-operative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [309]. Subsequent meta-analyses supported these conclusions [303, 310-313, 323]; however, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [309]. The largest meta-analysis published to date, concluded that B-TURP compared to M-TURP reduced TUR syndrome and blood transfusion events by twenty and 28 fewer events per 1000 participants, respectively [308]. The study also concluded that B-TURP may carry a similar risk of UI and may result in similar rates of re-TURP in the short-term (four fewer events and one more re-TURP per 1000 participants, respectively) compared to M-TURP [308]. An RCT based meta-analysis has shown that TURis reduces the risk of TUR-syndrome and the need for blood transfusion compared to M-TURP [313]. It was concluded that TURis is associated with improved peri-operative safety, eliminating the risk of TUR syndrome, reducing the risk of blood transfusion/clot retention and hospital stay. No significant difference was detected in urethral stricture rates.

Data from the vast majority of individual RCTs with mid- to long-term follow-up (up to 60 months), showed no differences between M-TURP and B-TURP in urethral stricture/BNC rates [314-322], in accordance with all published meta-analyses. However, two individual RCTs have shown opposing results [321, 327]. A significantly higher stricture (urethral stricture + BNC) rate was detected in the B-TURP arm performed with a “quasi” bipolar system (TURis, Olympus Medical) in patients with a prostate volume > 70 mL at 36 months follow-up [321]. In addition, a significantly higher BNC, but not urethral stricture, rate was detected in the B-TURP arm performed with a “true” bipolar system (Gyrus PK SuperPulse, Olympus Medical) in 137 patients at twelve months follow-up [327].

Randomised controlled trials using the erectile function domain of the IIEF (IIEF-ED) and the ejaculatory domain of the male sexual-health questionnaire (Ej-MSHQ) showed that M-TURP and B-TURP have a similar effect on erectile and ejaculatory function [328, 329]. Comparative evaluations of the effects on overall sexual function, quantified with IIEF-15, showed no differences between B-TURP and M-TURP at twelve months follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [329, 330]. Furthermore, the largest meta-analysis published to date, showed that erectile function measured by IIEF-5 appears to be similar at twelve months follow-up after B-TURP and M-TURP [308].

A comparative study [331] evaluated the safety of B-TURP in patients taking therapeutic oral anticoagulation (phenprocoumon) or anti-platelet drug therapy (acetylsalicylic acid or clopidogrel), without stopping or bridging the medication. Outcomes under acetylsalicylic acid were comparable to the unmedicated control group. Under oral anticoagulation therapy catheterisation (median 41-hours vs. 24-hours) and hospitalisation time was longer (median four days vs. three days), AUR rate was higher (18% vs. 6%), but blood transfusion rates did not differ to the control group. Under anti-platelet therapy blood transfusion (19% vs. 1%) and re-hospitalisation rates (19% vs. 3%) were higher.

Practical considerations: Monopolar-TURP is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (30-80 mL suitable for M-TURP). No studies on the optimal cut-off value exist, but the complication rates increase with prostate size [325]. The upper limit for M-TURP is suggested as 80 mL (based on Panel consensus, under the assumption that this limit depends on the surgeon's experience, choice of resectoscope size and resection speed), as surgical duration increases, there is a significant increase in the rate of complications and the procedure is safest when performed in under 90 minutes [332].

Bipolar TURP in patients with moderate-to-severe LUTS secondary to BPO, has similar efficacy with M-TURP, but lower peri-operative morbidity. The duration of improvements with B-TURP were documented in a number of RCTs with mid-term follow-up. Long-term results (up to five years) for B-TURP showed that safety and efficacy are comparable to M-TURP [314-322]. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

Summary of evidence	**LE**
Bipolar- or monopolar-TURP is the current standard surgical procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO.	1a
Bipolar-TURP achieves short-, mid- and long-term results comparable with M-TURP, but B-TURP has a more favourable peri-operative safety profile.	1a

Recommendation	**Strength rating**
Offer bipolar- or monopolar-transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Strong

5.3.1.2 Holmium laser resection of the prostate

With the advent of holmium laser enucleation of the prostate (section 5.3.2.3) and the fact that no relevant publications on holmium laser resection of the prostate (HoLRP) have been published since 2004, HoLRP of the prostate does not play a role in contemporary treatment algorithms.

5.3.1.3 Thulium:yttrium-aluminium-garnet laser (Tm:YAG) vaporesection of the prostate

Mechanism of action: In the Tm:YAG laser, a wavelength between 1,940 and 2,013 nm is emitted in continuous wave mode. The laser is primarily used in front-fire applications [333]. Different applications such as vaporesection (ThuVARP) have been published [334].

Efficacy: Several meta-analyses with pooled data from both RCTs and non-RCTs have evaluated ThuVARP vs. M-TURP [335-337], and B-TURP [338-340]. The largest meta-analyses included nine RCTs and seven non-RCTs and reported no clinically relevant differences in efficacy (IPSS, QoL score and Q_{max}) between ThuVARP and M-TURP or B-TURP at twelve months [339]. A multicentre, RCT with 410 men reported that ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at twelve months follow-up [341]. The beneficial effect of TURP in terms of Q_{max} was strengthened in men aged < 70 years and in those diagnosed with LUTS rather than urinary retention. No differences in individual patient-reported urinary symptoms were seen between arms, with the exception of some evidence to indicate potential reduction in nocturia in the TURP arm. Data from one RCT with long-term follow-up showed no difference in efficacy and re-operation rates between ThuVARP and M-TURP (2.1% vs. 4.1%, respectively) [342]. A prospective multicentre study on ThuVARP, including 2,216 patients, showed durable post-operative improvement in IPSS, QoL, Q_{max}, and PVR for the entire eight years of follow-up [343].

Tolerability and safety: In a number of meta-analyses longer operation times, shorter catheterisation/hospitalisation times and less blood loss without significant differences in transfusion rates or in any other short-term complication rates have been reported for ThuVARP compared to TURP [335-340]. A significantly higher transfusion rate was reported after M-TURP in two meta-analyses [337, 339]. However, overall RCT quality was relatively low with limited follow-up potentially accounting for under-reporting of late complications,

such as urethral stricture/BNC [339]. A multicentre RCT with 410 men, followed up for twelve months reported that ThuVARP and TURP show similar operation, catheterisation, and hospitalisation times between arms with no difference in the frequency or severity of surgical complications or in blood transfusions rate or haemoglobin change [341, 344]. Patients with urinary retention had similarly positive outcomes to those with LUTS [341, 344]. Data from three RCTs with mid- to long-term follow-up (18 to 48 months) showed no differences in late complication rates between ThuVARP and TURP (BNC: 0.0%-2.1% vs. 0.0%-4.1%; stricture: 0.0%-2.2% vs. 0.0%-2.2%, respectively) [342, 345, 346].

Haemoglobin drop was significantly higher in the bridging group in a retrospectively analysed case series of 103 patients who underwent ThuVARP and received either low molecular weight heparin bridging or continued antiplatelet/anticoagulant therapy [347].

Practical considerations: As a limited number of RCTs with mid- to long-term follow-up support the efficacy of ThuVARP, there is a need for ongoing investigation of the technique.

Summary of evidence	**LE**
Laser vaporesection of the prostate using Tm:YAG laser (ThuVARP) has similar operation, catheterisation and hospitalisation times compared to TURP. ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at twelve months follow-up. ThuVARP and TURP show similar short-term safety. Mid- to long-term results on efficacy and safety compared to TURP are very limited.	1b

Recommendation	**Strength rating**
Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to TURP.	Weak

5.3.1.4 Transurethral incision of the prostate

Mechanism of action: Transurethral incision of the prostate (TUIP) involves incising the bladder outlet without tissue removal. Transurethral incision of the prostate is conventionally performed with Collins knife using monopolar electrocautery; however, alternative energy sources such as holmium laser may be used [348]. This technique may replace M-TURP in selected cases, especially in prostate sizes < 30 mL without a middle lobe.

Efficacy: An RCT comparing conventional TUIP vs. TUIP using holmium laser in prostates ≤ 30 mL with a follow-up of twelve months, found both procedures to be equally effective in relieving BOO with similarly low re-operation rates [348]. A meta-analysis of ten RCTs found similar LUTS improvements and lower but significant improvements in Q_{max} for TUIP [349]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30 mL and three < 60 mL. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after M-TURP (7.2%) [349].

Tolerability and safety: An RCT comparing conventional TUIP vs. TUIP using holmium laser reported both procedures to be safe with low complication rates; however, the operation time and retrograde ejaculation rate was significantly lower in the conventional TUIP arm [348]. No cases of TUR-syndrome have been recorded after TUIP. The risk of bleeding after TUIP is small [349].

Practical considerations: Transurethral incision of the prostate is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice between M-TURP and TUIP should be based primarily on prostate volume (< 30 mL TUIP) [349].

Summary of evidence	**LE**
Transurethral incision of the prostate shows similar efficacy and safety to M-TURP for treating moderate-to-severe LUTS secondary to BPO in men with prostates < 30 mL.	1a
No case of TUR-syndrome has been recorded, the risk of bleeding requiring transfusion is negligible and retrograde ejaculation rate is significantly lower after TUIP, but the re-operation rate is higher compared to M-TURP.	1a
The choice between TUIP and TURP should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively).	4

Recommendation	**Strength rating**
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	Strong

5.3.2 ***Enucleation of the prostate***

5.3.2.1 *Open prostatectomy*

Mechanism of action: Open prostatectomy is the oldest surgical treatment for moderate-to-severe LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure). It is used for substantially enlarged glands (> 80-100 mL).

Efficacy: Open prostatectomy reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q_{max} by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98%. Efficacy is maintained for up to six years [350-355]. Data from an Austrian nationwide study of 1,286 men submitted to OP showed that the endourological re-intervention rates after primary OP were 0.9%, 3.0%, 6.0%, and 8.8%, at three months, one year, five years, and eight years, respectively. The respective incidence of re-TURP was 0.5%, 1.8%, 3.7% and 4.3%, respectively [9].

Two meta-analyses [356, 357] evaluated the overall efficacy of OP performed via a transvesical approach vs. two transurethral enucleation techniques for treating patients with large glands, namely bipolar transurethral enucleation of the prostate (B-TUEP) and holmium laser enucleation of the prostate (HoLEP). The larger study included nine RCTs involving 758 patients [357]. Five RCTs compared OP with B-TUEP [355, 358-361] and four RCTs compared OP with HoLEP [350, 351, 362, 363]. At three, six, twelve and 24-months follow-up there were no significant differences in Q_{max} [357]. Post-void residual, PSA, IPSS and QoL score showed no significant differences at one-, three-, six- and twelve-months follow-up [357]. Randomised controlled trials indicate that OP is as effective as HoLEP for improving micturition in large prostates [350, 351], with similar improvement regarding Q_{max}, IPSS score and re-operation rates after five years [350].

Tolerability and safety: Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [354]. Data from an Austrian nationwide study of 1,286 men submitted to OP showed mortality rates of 0.2% at 30 days and 0.4% at 90 days [307]. The estimated transfusion rate is about 7-14% [350, 353, 354, 356]. Long-term complications include transient UI (up to 10%), BNC and urethral stricture (about 6%) [350-352, 356, 364].

Two meta-analyses evaluated the overall safety of OP performed via a transvesical approach vs. B-TUEP and HoLEP [356, 357]. Operation time did not differ significantly between OP and B-TUEP but was significantly shorter for OP compared to HoLEP. Catheterisation and hospitalisation time were significantly longer for OP, which was also associated with more blood transfusions. There were no significant differences regarding other complications. There was no significant difference in IIEF-5 at three, six, twelve and 24-months follow-up.

Practical considerations: Open prostatectomy is the most invasive surgical method, but it is an effective and durable procedure for the treatment of LUTS/BPO. In the absence of an endourological armamentarium including a holmium laser or a bipolar system and with appropriate patient consent, OP is a reasonable surgical treatment of choice for men with prostates > 80 mL.

Summary of evidence	**LE**
Open prostatectomy is an effective and durable procedure for the treatment of LUTS/BPO, but it is the most invasive surgical method.	1b
Open prostatectomy shows similar short- and mid-term efficacy to B-TUEP and HoLEP for treating moderate-to-severe LUTS secondary to BPO in patients with large prostates.	1a
Open prostatectomy has a less favourable peri-operative safety profile compared to B-TUEP and HoLEP.	1a
The long-term functional results of OP are comparable to HoLEP.	1b

Recommendation	**Strength rating**
Offer open prostatectomy in the absence of bipolar transurethral enucleation of the prostate and holmium laser enucleation of the prostate to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	Strong

5.3.2.2 *Bipolar transurethral enucleation of the prostate)*

Mechanism of action: Following the principles of bipolar technology (section 5.3.1.1), the obstructive adenoma is enucleated endoscopically by the transurethral approach. Bipolar-transurethral enucleation of the prostate (B-TUEP) evolved from plasmakinetic (PK) B-TURP and was introduced by Gyrus ACMI. The technique, also referred to as PK enucleation of the prostate (PKEP), utilises a bipolar high-frequency generator and

a variety of detaching instruments, for this true bipolar system, including a point source in the form of a axipolar cystoscope electrode suitable for enucleation [365] or a resectoscope tip/resection loop [366, 367]. More recently, a novel form of B-TUEP has been described, bipolar plasma enucleation of the prostate (BPEP), stemming from B-TURP (TURis, Olympus Medical), that utilises a bipolar high frequency generator and a variety of detaching instruments including a mushroom- or button-like vapo-electrode [361, 368] and a Plasmasect enucleation electrode [369] for this quasi-bipolar system. Bipolar transurethral enucleation of the prostate is followed by either morcellation [361, 365] or resection [366-368, 370-372] of the enucleated adenoma.

Efficacy: One RCT evaluating PKEP vs. M-TURP in 204 patients with mean prostate volume < 80 mL reported a significant improvement in IPSS, QoL score, and Q_{max}, with urodynamically proven de-obstruction favouring PKEP at 36 months follow-up [367]. The RCT concluded that the mid-term clinical efficacy of PKEP was comparable to M-TURP [367]. One RCT evaluating PKEP vs. B-TURP in patients with prostate volume > 80 mL reported no clinically relevant differences in IPSS, QoL score, and Q_{max}, at six months follow up [373]. Another RCT evaluating BPEP vs. B-TURP in patients with prostate volume > 80 mL reported not clinically relevant differences in IPSS, QoL score, Q_{max} and PVR at 24 months follow-up [374]. Two meta-analyses, reported similar efficacy at twelve months in terms of IPSS, QoL score and Q_{max} for B-TUEP (PKEP or BPEP) vs. B-TURP [375, 376]. Another meta-analysis evaluating B-TUEP vs. B-TURP, reported similar efficacy at 36 months in terms of IPSS, and Q_{max} [323]. Two RCTs evaluated the mid-term efficacy of PKEP vs. B-TURP at 36 months [366, 371] and one RCT evaluated long-term efficacy at 60 months [372]. Efficacy was significantly better for PKEP in patients with large prostates at 36, 48 and 60 months [366, 372]. Comparative data on efficacy for B-TUEP vs. OP and the various forms of laser enucleation are presented in section 5.3.2.1 – 5.3.2.5, respectively.

Tolerability and safety: An RCT evaluating PKEP vs. M-TURP in patients with prostate volume < 80 mL and 36-month follow-up reported that PKEP is superior to M-TURP in terms of haemoglobin drop, irrigation, catheterisation, and hospitalisation time [367]. No significant differences between the arms were reported in operation time, blood transfusion rates, sexual function, or any other reported complications (TUR-syndrome, clot retention, incontinence, retrograde ejaculation, urethral structures/BNC) [367]. One RCT evaluating PKEP vs. B-TURP in patients' prostate volume > 80 mL and six months follow-up reported that PKEP is superior to B-TURP in terms of operation, irrigation, catheterisation, hospitalisation time and haemoglobin drop [373]. Significant differences were reported in blood transfusion, BNC and retrograde ejaculation rates favouring PKEP, but no differences in urethral stricture and ED rates were reported [373]. Another RCT evaluating BPEP vs. B-TURP in patients with prostate volume > 80 mL reported that BPEP had longer operative time but shorter irrigation, catheterisation, hospitalisation time and lower haemoglobin drop with no differences in blood transfusion, urethral stricture and UI rates at 24 months follow-up [374]. A meta-analysis evaluating PKEP vs. TURP reported that mid-term IIEF-5 scores were comparable [377]. Another meta-analysis reported less bleeding with B-TUEP compared to M-TURP but similar UI rates and AUR after catheter removal [323]. Two meta-analyses evaluating B-TUEP vs. B-TURP reported similar operation, catheterisation and hospitalisation times; lower acute urine retention rates; significantly reduced haemoglobin drop and blood transfusion rates; no difference in erectile function; and no difference in all other reported complication rates including urethral stricture/BNC rates for B-TUEP at 24 months follow-up [375, 376]. No difference in urethral stricture/BNC rates was reported at 60 months follow-up [372]. Comparative data on efficacy for B-TUEP vs. OP and the various forms of laser enucleation are presented in section 5.3.2.1 – 5.3.2.5, respectively.

Summary of evidence	**LE**
Bipolar transurethral (plasmakinetic) enucleation of the prostate shows favourable mid- to long-term efficacy compared to TURP.	1b
Bipolar transurethral (plasmakinetic) enucleation of the prostate has a favourable peri-operative safety profile and demonstrates similar mid- to long-term safety compared to TURP.	1b

Recommendation	**Strength rating**
Offer bipolar transurethral (plasmakinetic) enucleation of the prostate to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate.	Weak

5.3.2.3 Holmium laser enucleation of the prostate

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis [378].

Efficacy: An initial meta-analysis reported no significant differences in short-term efficacy (Q_{max}) and re-intervention rates (4.3% vs. 8.8%) between HoLEP and M-TURP [379]; however, subsequent meta-analyses reported favourable short-term efficacy (Q_{max} and IPSS) for HoLEP [303, 336, 375, 380]. Another meta-analysis reported similar efficacy at 24 months in terms of IPSS, and Q_{max} [323]. Three meta-analyses evaluating HoLEP vs. B-TURP showed no significant differences in short-term efficacy (IPSS, QoL score and Q_{max}) [323, 375, 381]. One RCT comparing HoLEP with M-TURP in a small number of patients with mean prostate volume < 80 mL and a seven year follow-up found that the functional long-term results were comparable [382]. One RCT comparing HoLEP with B-TURP in patients with prostate volume < 80 mL reported no significant difference in IPSS, QoL score and Q_{max} at 24 months [383]. Long-term (72 months) improvement in IPSS and Q_{max} was better for HoLEP, but there were no clinically relevant differences between the arms [384]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported no significant difference in IPSS, QoL score and Q_{max} at 36 months, however, the overall re-treatment rate was significantly lower following HoLEP with less patients restarting α-blockers and less re-operations [385]. Comparative efficacy data for HoLEP vs. OP is presented in section 5.3.2.1. One small RCT evaluating HoLEP vs. PKEP in patients with mean prostate volume < 80 mL reported similar improvements in IPSS and Q_{max} as well as similar re-operation rates at twelve months follow-up [365]. An RCT comparing HoLEP vs. bipolar EEP reported no significant difference in IPSS, QoL score, PVR, and Q_{max} at one, three-, and twelve-months follow-up [386].

Tolerability and safety: Data from a large national database on peri-operative outcomes of 2,869 laser enucleation of the prostate and 37,577 TURP procedures supports that laser enucleation of the prostate is associated with longer operation times, shorter hospitalisation times, similar complication rates (including transfusions, and re-operations), but lower rates of infectious complications [387]. Several meta-analyses found that HoLEP has longer operation times, shorter catheterisation and hospitalisation times, reduced blood loss, fewer blood transfusions but no significant differences in urethral strictures (2.6% vs. 4.4%) and stress urinary incontinence (SUI) (1.5% vs. 1.5%) rates compared to M-TURP [336, 375, 379, 380, 388]. Another meta-analysis reported that HoLEP has shorter catheterisation times, lower haemoglobin drops, fewer blood transfusions, urethral strictures and UTIs but no significant differences in clot retention rates and AUR after catheter removal compared to M-TURP [323]. Three meta-analyses evaluated HoLEP vs. B-TURP [375, 381, 389]. One, reported longer operation times for HoLEP, but no significant differences in hospitalisation time or complication rates [375] whilst another reported no significant differences in operation and catheterisation times or short-term complication rates [381]. A SR reported that HoLEP has lower AUR rates after catheter removal but similar haemoglobin drop, UTI, urethral stricture, and UI rates [323]. A RCT comparing HoLEP with B-TURP in patients with prostate volume < 80 mL reported longer operation time, shorter catheterisation and hospitalisation times and a lower risk for haemorrhage for HoLEP with no significant differences in blood transfusion rates or other complication rates at 24 months [383]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported shorter operation, catheterisation and hospitalisation times and lower blood transfusion rates for HoLEP but no differences in complication rates including UI and IIEF-5 score at 36 months [385]. Comparative data on safety of HoLEP vs. OP are presented in section 5.3.2.1. One small RCT evaluating HoLEP vs. PKEP in patients with mean prostate volume < 80 mL reported significantly shorter operation times for HoLEP, but similar catheterisation and hospitalisation times and complication rates at twelve months follow-up [365]. An RCT comparing HoLEP vs. bipolar B-TUEP demonstrated shorter operation and hospitalisation times and earlier catheter removal for HoLEP [386].

An RCT of pulse modulation in HoLEP (Virtual basket) demonstrated significantly less haemoglobin drop and reduced operation times when compared to conventional HoLEP [390].

Holmium laser enucleation of the prostate has been safely performed in patients using anticoagulant and/or antiplatelet medications [391, 392]. However, current limitations include: a lack of RCTs; limited data on short- and mid-term complications and bridging therapy; data presentation does not allow for separate interpretation of either antiplatelet and anticoagulant therapy.

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP [393, 394]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP. Data have shown that ejaculation and orgasm perception are the two most impacted domains after HoLEP [395]. Attempts to maintain ejaculatory function with HoLEP have been reported to be successful in up to 46.2% of patients [396].

A meta-analysis of seven RCTs evaluating HoLEP vs. TURP reported that short- and mid-term IIEF-5 scores were comparable, whilst long-term scores were significantly better for HoLEP [397]. Two other meta-analyses detected no difference in mid-term retrograde ejaculation rates [398].

An RCT comparing HoLEP vs B-TUEP, reported shorter operation and hospitalisation times and earlier catheter removal for HoLEP [386].

Practical considerations: Holmium laser enucleation of the prostate requires experience and relevant endoscopic skills. The experience of the surgeon is the most important factor affecting the overall occurrence of complications [399, 400]. Mentorship programmes are advised to improve surgical performance from both an institutional and personal learning curve perspective [401-403].

Summary of evidence	LE
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates similar mid- to long-term efficacy when compared to TURP.	1b
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates similar short-term safety when compared to TURP.	1a
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates longer operation times, but a more favourable peri-operative profile when compared to TURP.	1a

Recommendation	Strength rating
Offer laser enucleation of the prostate using Ho:YAG laser (HoLEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate or open prostatectomy.	Strong

5.3.2.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG) enucleation of the prostate

Mechanism of action: The Tm:YAG laser has been described in section 5.3.1.3. Enucleation using the Tm:YAG laser includes ThuVEP (vapoenucleation i.e. excising technique) and ThuLEP (blunt enucleation).

Efficacy: Two meta-analyses evaluating ThuLEP vs. M-TURP and B-TURP reported no clinically relevant differences in short-term efficacy (Q_{max}, IPSS and QoL score) [323, 375]. An RCT with five years follow-up comparing ThuLEP with B-TURP found no difference between the two procedures for Q_{max}, IPSS, PVR, and QoL [404]. A meta-analysis [405] evaluating ThuLEP vs. HoLEP showed no clinically relevant differences in IPSS, QoL score and Q_{max} at twelve months in accordance with one RCT showing similar results at eighteen months [406]. Furthermore, ThuLEP and PKEP were compared in one RCT with twelve months follow-up the outcome of which showed no difference with regard to efficacy [407]. There are mainly prospective case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [408-411]. A cohort study with median follow-up of 36.5 months reported improved Q_{max} (19.1 vs. 7.75 mL/s), PVR (31.9 vs. 150 mL), IPSS (4.5 vs. 24), and QoL scores (1 vs. 5), with a PSA reduction of 86.5% [412].

Tolerability and safety: Two meta-analyses evaluating ThuLEP vs. M-TURP and B-TURP reported a longer operation time and shorter catheterisation time for ThuLEP compared to M-TURP and a shorter hospitalisation time for ThuLEP compared to B-TURP [323, 375]. Lower blood transfusion rates compared to M-TURP, lower clot retention rates compared to B-TURP, and no difference in the other complication rates were also reported for ThuLEP [323, 375]. An RCT comparing ThuLEP with B-TURP reported a significant difference in IIEF-5 score favouring ThuLEP at twelve months [413]. A meta-analysis evaluating ThuLEP vs. HoLEP showed significantly lower haemoglobin drop for ThuLEP [405]. Transient UI was more common for HoLEP. Intra-operatively ThuLEP showed shorter operation times when compared to HoLEP [375] and a multicenter RCT demonstrated lower haemoglobin loss for ThuLEP compared to HoLEP [390].

Another meta-analysis [414] evaluating ThuLEP vs. HoLEP showed a significant difference is enucleation time favouring ThuLEP, but no significant differences in operation, catheterisation and hospitalisation times and short-term complication rates. These results were in accordance with one RCT showing similar results, including no urethral and bladder neck strictures, at eighteen months [406]. ThuLEP and PKEP were compared in one RCT with twelve months follow-up [407]. No significant difference in complication rates was detected, but haemoglobin level decrease and catheterisation time was significantly lower for ThuLEP.

In comparative studies ThuVEP shows high intra-operative safety [415], also in case series of patients with large prostates [408] and anticoagulation or bleeding disorders [409, 410]. In a cohort study on ThuVEP, UTIs occurred in two patients, urethral stricture and BNC developed in one patient each, respectively and one patient was treated for recurrent adenoma of the prostate [412]. A study focusing on post-operative complications after ThuVEP reported adverse events in 31% of cases, with 6.6% complications greater then Clavien grade 2 [416]. One case control study on ThuVEP with 48-month follow-up reported long-term durability of voiding improvements and overall re-operation rates of 2.4% [410]. Two studies addressed the impact of ThuVEP on sexual function, demonstrating no effect on erectile function with increased prevalence of retrograde ejaculation post-operatively [417, 418].

Practical considerations: ThuLEP seems to offer similar efficacy and safety when compared to TURP, bipolar enucleation and HoLEP; whereas, ThuVEP is not supported by RCTs. Based on the limited number of RCTs there is a need for ongoing investigation of these techniques.

Summary of evidence	LE
Enucleation of the prostate using the Tm:YAG laser demonstrates similar efficacy when compared to M-TURP/bipolar transurethral (plasmakinetic) enucleation, HoLEP and B-TURP in the short-, mid-, and long-term, respectively.	1b
Enucleation of the prostate using the Tm:YAG laser (ThuLEP) demonstrates similar safety compared to TURP/bipolar transurethral (plasmakinetic) enucleation, and HoLEP in the short- and mid-term, respectively.	1b
Vapoenucleation of the prostate using a Tm:YAG laser (ThuVEP) seems to be safe in patients with large prostates and those receiving anticoagulant or antiplatelet therapy.	2b

Recommendations	Strength rating
Offer enucleation of the prostate using the Tm:YAG laser (ThuLEP, ThuVEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate, holmium laser enucleation or bipolar transurethral (plasmakinetic) enucleation.	Weak
Offer Tm:YAG laser enucleation of the prostate to patients receiving anticoagulant or antiplatelet therapy.	Weak

5.3.2.5 Diode laser enucleation of the prostate (DiLEP)

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1,318, and 1,470 nm (depending on the semiconductor used) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [385].

Efficacy: One small RCT comparing 1,318 nm DiLEP with B-TURP in patients with mean prostate volume < 80 mL reported no significant differences in IPSS, QoL score, Q_{max} and PVR at six months follow-up [419]. Another RCT comparing 1,470 nm DiLEP with B-TURP in 157 patients with mean prostate volume < 80 mL also reported no significant differences in IPSS, QoL score, Q_{max} and PVR at twelve months follow-up [420]. In addition, three RCTs comparing 980 nm DiLEP with PKEP in patients with mean prostate volume < 80 mL [421, 422] and > 80 mL [423] reported no significant differences in IPSS, QoL score, Q_{max} and PVR at twelve months follow-up. An RCT of DilEP (980 nm) vs. HoLEP detected no significant difference in Q_{max}, PVR, IPSS, and QoL at three, six and twelve months follow-up [424].

Tolerability and safety: One small RCT comparing 1,318 nm DiLEP with B-TURP in patients with mean prostate volume < 80 mL and six months follow-up reported a significantly longer operation time for DiLEP, but shorter catheterisation and hospitalisation times, as well as less blood loss (without differences in blood transfusion rates) [419]. No differences in complication rates were reported between the two arms [419]. Another RCT comparing 1,470 nm DiLEP with B-TURP in 157 patients with prostate volume < 80 mL and twelve months follow-up reported significantly shorter operation, catheterisation, and hospitalisation times with less blood loss (without differences in blood transfusion rates) for DiLEP, with no differences in complication rates between the two arms [420]. Three RCTs comparing 980 nm DiLEP with PKEP in patients with prostate volume < 80 mL [421, 422] and > 80 mL [423] and twelve months follow-up reported conflicting peri-operative outcomes: operation time (no difference between arms [421], significanly shorter for DiLEP [422] or sgnificanly longer for DiLEP [423]); catheterisation time (no difference between the two arms [421], significanly shorter for DiLEP [422, 423]); hospitalisation time (no difference between arms [421, 422], significanly shorter for DiLEP [423]); blood loss (no difference in haemoglobin drop between arms [421], significantly lower haemoglobin drop for DiLEP [422, 423]). All trials reported no differences in blood transfusion rates and complication rates [421-423]. An RCT of DiLEP (980 nm) vs. HoLEP with twelve months follow-up demonstrated no significant difference in peri-operative outcomes including operation and hospitalisation times, resected tissue weight and catheter duration with the DiLEP group also showing lower haemoglobin drop [424].

Practical considerations: Diode laser enucleation seems to offer similar efficacy and safety when compared to either B-TURP or bipolar transurethral (plasmakinetic) enucleation. Based on the limited number of mainly low-quality RCTs, and controversial data on the retreatment rate, results for DiLEP should be evaluated in further higher quality RCTs.

Summary of evidence	LE
Laser enucleation of the prostate using the 1,318 nm or 1,470 laser showed comparable short-term efficacy and safety to B-TURP. Peri-operative parameters like blood loss, catheterisation time and hospital stay are in favour of diode enucleation.	1b
Laser enucleation of the prostate using the 980 nm laser showed comparable short-term efficacy and safety to bipolar transurethral (plasmakinetic) enucleation.	1b

Recommendation	Strength rating
Offer 120-W 980 nm, 1,318 nm or 1,470 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to bipolar transurethral (plasmakinetic) enucleation or bipolar transurethral resection of the prostate.	Weak

5.3.2.6 Enucleation techniques under investigation

5.3.2.6.1 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [425], while the first RASP was reported in 2008 [426]. Both LSP and RASP are performed using different personalised techniques, based on the transcapsular (Millin) or transvesical (Freyer) techniques of OP.

Efficacy: A SR and meta-analysis showed that in 27 observational studies including 764 patients, the mean increase in Q_{max} was 14.3 mL/s, and the mean improvement in IPSS was 17.2 [427]. There were no differences in improvements in Q_{max} and IPSS [427]. A meta-analysis comparing MISP vs. OP reported no significant differences with regard to functional and symptom parameters between the two techniques [428]. A multicentre RCT with median follow-up of 26 months did not demonstrate any significantly different functional or peri-operative results between LSP, RASP and HoLEP [429].

Two recent retrospective series on RASP were not included in the meta-analysis which confirm these findings [430, 431]. The largest retrospective series reports 1,330 consecutive cases including 487 RASP (36.6%) and 843 LSP (63.4%) cases. The authors confirm that both techniques can be safely and effectively done in selected centres [430].

Tolerability and safety: In the largest series, the post-operative complication rate was 10.6% (7.1% for LSP and 16.6% for RASP), most of the complications being of low grade. The most common complications in the RASP series were haematuria requiring irrigation, UTI and AUR; in the LSP series, the most common complications were UTI, ileus and AUR. In the most recent, largest comparative analysis of robotic vs. OP for large-volume prostates, a propensity score-matched analysis was performed with five covariates. Robotic compared with OP demonstrated a significant shorter average length of hospital stay, but longer mean operative time. The robotic approach was also associated with a lower estimated blood loss. Improvements in maximal flow rate, IPSS, QoL, PVR and post-operative PSA levels were similar before and after surgery for both groups. There was no difference in complications between the groups [432]. In a multicentre RCT comparing LSP, RASP and HoLEP LSP demonstrated significantly longer catheterisation times than RASP and HoLEP, whilst RASP and LSP showed longer hospitalisation times and lower rates of *de novo* bladder storage symptoms [429]. A meta-analysis comping MISP vs. OP demonstrated shorter hospital stay, irrigation time, as well as blood loss and transfusion rates for MISP [428]. A SR and meta-analysis reported the mean duration of operation was 141 minutes and the mean intra-operative blood loss was 284 mL. One hundred and four patients (13.6%) developed a surgical complication. In comparative studies to OP, length of hospital stay, length of catheter use, and estimated blood loss were significantly lower in the MISP group, while the duration of operation was longer. There were no differences in peri-operative complications between both procedures [427].

Practical considerations: Minimal invasive simple prostatectomy seems comparable to OP in terms of efficacy and safety, providing similar improvements in Q_{max} and IPSS [427]. However, most studies are of a retrospective nature. High-quality studies are needed to compare the efficacy, safety, and hospitalisation times of MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated.

Summary of evidence	LE
Minimal invasive simple prostatectomy is feasible in men with prostate sizes > 80 mL needing surgical treatment; however, RCTs are needed.	2a

5.3.2.6.2 532 nm ('Greenlight') laser enucleation of the prostate

Mechanism of action: The Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue. Three "Greenlight" lasers exist, which differ not only in maximum power output, but more significantly in fibre design and the associated energy tissue interaction of each. The standard Greenlight device today is the 180-W XPS laser, but the majority of evidence is published with the former 80-W KTP or 120-W HPS (LBO) laser systems.

Two approaches for KTP/LBO laser-based enucleation technique exist [433]. GreenLEP is an anatomical enucleation technique following the principle of blunt dissection of the adenoma with the sheath and laser energy for incision as described for ThuLEP [434]. *En bloc* GreenLEP preparation has been popularised with the same approach. A variation of the most commonly applied GreenLEP technique, with tissue morcellation, is the *in-situ* vaporisation of apically enucleated tissue, also referred to as anatomic vaporisation-incision technique [434, 435]. To date, no RCTs evaluating enucleation using the KTP/LBO laser have been carried out [436].

*5.3.3 **Vaporisation of the prostate***

5.3.3.1 Bipolar transurethral vaporisation of the prostate

Mechanism of action: Bipolar transurethral vaporisation of the prostate (B-TUVP) was introduced in the late 1990s ("PK" B-TUVP). The technique was derived from PK B-TURP and utilised a bipolar electrode and a high-frequency generator to create a plasma effect able to vaporise prostatic tissue [437]. With minimal direct tissue contact (near-contact; hovering technique) and heat production the bipolar electrode produces a constant plasma field (thin layer of highly ionized particles; plasma corona), allowing it to glide over the tissue and vaporise a limited layer of prostate cells without affecting the underlying tissue whilst achieving haemostasis, leaving behind a TURP-like cavity [438]. A distinct difference between B-TUVP and its ancestor (monopolar TUVP), is that B-TUVP displays thinner (< 2 mm) coagulation zones [439], compared to the disproportionate extent of those created by the former (up to 10 mm) [440], potentially resulting in mostly irritative side-effects and SUI [439, 441, 442].

Efficacy: Bipolar-TUVP has been evaluated as a TURP alternative for treating moderate-to-severe LUTS in thirteen RCTs, including a total of 1,244 men with a prostate size of < 80 mL [317, 443-454]. Early RCTs evaluated the PK B-TUVP system [443-447]; however, during the last decade, only the "plasma" B-TUVP system with the "mushroom- or button-like" electrode (Olympus, Medical) has been evaluated [317, 448-454]. Results have been pooled in three meta-analyses [303, 455, 456], and a narrative synthesis has been produced in two SRs [303, 457]. The follow-up in most RCTs is twelve months [443-446, 448-450, 452, 454]. The longest follow-up is 36 months in a small RCT (n = 40) and eighteen months in a subsequent RCT (n = 340); evaluating PK [447] and plasma B-TUVP [317], respectively.

Early pooled results concluded that no significant differences exist in short-term efficacy (IPSS, QoL score, Q_{max} and PVR) between PK B-TUVP and TURP [303]. However, the promising initial efficacy profile of the former may be compromised by inferior clinical outcomes (IPSS and Q_{max}) at mid-term. Larger RCTs with longer follow-up are necessary to draw definite conclusions [303, 447]. A SR of seven RCTs comparing PK and plasma B-TUVP with TURP concluded that functional outcomes of B-TUVP and TURP do not differ [457]. The poor quality of the included RCTs and the fact that most data was derived from a single institution was highlighted [457]. A similar SR of eight RCTs comparing both B-TUVP techniques with TURP concluded that: not enough consistent data suitable for a meta-analysis exists; that the main functional results are contradictory; and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions [303]. A meta-analysis comparing B-TUVP with TURP reported similar efficacy at twelve-month follow-up in terms of IPSS, and Q_{max} [323]. A meta-analysis of six RCTs specifically evaluating plasma B-TUVP vs. TURP, concluded that both techniques result in a similar improvement of LUTS [456].

Tolerability and safety: Early pooled results concluded that no statistically significant differences exist for intra-operative and short-term complications between PK B-TUVP and TURP, but peri-operative complications are significantly fewer after B-TUVP [303]. However, the results of a statistical analysis comparing pooled specific complication rates were not directly reported in this meta-analysis [303]. Mid-term safety results (urethral stricture, ED, and retrograde ejaculation) have also been reported to be similar [447], but larger RCTs with longer follow-up are necessary to draw definite conclusions [303, 447]. A SR of seven RCTs comparing PK and plasma B-TUVP with TURP concluded that most RCTs suggest a better haemostatic efficiency for B-TUVP, resulting in shorter catheterisation (42.5 vs. 77.5 hours) and hospitalisation times (3.1 vs. 4.4 days) [457]. A similar SR of eight RCTs comparing both B-TUVP techniques with TURP concluded that not enough consistent data suitable for a meta-analysis exists and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions [303]. A meta-analysis reported that B-TUVP has

shorter and similar catheterisation time compared to M-TURP and B-TURP, respectively; lower haemoglobin drop compared to either TURP technique; significantly fewer clot retentions/blood transfusions compared to M-TURP but not B-TURP; and no difference in other complication rates compared to either TURP technique [323]. A meta-analysis of six RCTs specifically evaluating plasma B-TUVP vs. TURP, concluded that no significant differences exist between the techniques in overall complication and transfusion rates [456]. However, a statistically significant difference was detected in major complication rates (Clavien 3, 4); including urethral stricture, severe bleeding necessitating re-operation and UI) and in the duration of catheterisation favouring plasma B-TUVP.

Practical considerations: Bipolar-TUVP and TURP have similar short-term efficacy. Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety, but inferior mid-term efficacy compared to TURP. Plasma B-TUVP has lower short-term major morbidity compared to TURP. Randomised controlled trials of higher quality, multicentre RCTs, and longer follow-up periods are needed to evaluate B-TUVP in comparison to TURP.

Summary of evidence	**LE**
Bipolar-TUVP and TURP have similar short-term efficacy.	1a
Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP.	1a
Plasma B-TUVP has a lower short-term major morbidity rate compared to TURP.	1a

Recommendation	**Strength rating**
Offer bipolar transurethral vaporisation of the prostate as an alternative to transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with a prostate volume of 30-80 mL.	Weak

5.3.3.2 532 nm ('Greenlight') laser vaporisation of the prostate

Mechanism of action: The Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers have been described in section 5.3.2.6.2.

Efficacy: A meta-analysis of the nine available RCTs comparing photoselective vaporisation of the prostate (PVP) using the 80-W and 120-W lasers with TURP was performed in 2012 [458]. No differences were found in Q_{max} and IPSS between 80-W PVP and TURP, but only three RCTs provided sufficient twelve-month data to be included in the meta-analysis [459-461]. Another meta-analysis from 2016 of four RCTs including 559 patients, on the 120-W laser, demonstrated no significant difference in functional and symptomatic parameters at six-, twelve-, and 24-month follow-up when compared to TURP [462]. A meta-analysis of two RCTs reported similar efficacy of 120-W PVP, compared to M-TURP at 36-months follow-up [323].

The only available RCT for the 180-W laser reported non-inferiority to TURP in terms of IPSS, Q_{max}, PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. Efficacy outcomes were similar to TURP with stable results at 24 months follow-up [463].

The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 months and showed a comparable improvement in IPSS, Q_{max}, and PVR [464]. Comparable improvements in IPSS, QoL, Q_{max}, or urodynamic parameters were reported from two RCTs with a maximum follow-up of 24 months [460, 465]. A SR and meta-analysis of eleven RCTs comparing M-TURP with the 80-W KTP or 120-W HPS system found no significant difference with respect to IPSS and Q_{max} improvement [466].

One RCT comparing HoLEP to PVP, in patients with prostates > 60 mL, showed comparable symptom improvement, but significantly higher flow rates and lower PVR volume after HoLEP at short-term follow-up; in addition, PVP showed a 22% conversion rate to TURP [467].

One RCT compared B-TUVP with PVP with the 180-W XPS Laser. Comparable improvement in IPSS and Q_{max} were reported at 24 months follow-up [468].

Tolerability and safety: A meta-analysis of RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time, but shorter catheterisation time and length of hospital stay after PVP [303]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, UTI, meatal stenosis, urethral stricture, or bladder neck stenosis [303]. In a meta-analysis including trials with the 120-W laser, patients in the PVP group demonstrated significantly lower transfusion rates, shorter catheterisation time and shorter duration of hospital stay compared to TURP. Re-operation rates and operation time were in favour of TURP. No significant differences were demonstrated for treatment for urethral stricture, BNC, incidence of incontinence and UTI [462]. A SR and meta-analysis of eleven RCTs comparing M-TURP with the 80-W KTP or 120-W HPS system found that PVP was superior to M-TURP with regard to transfusion

rate, clot retention, catheterisation and hospitalisation time. A meta-analysis confirmed that PVP was superior to both M-TURP/B-TURP with regard to catheterisation and to M-TURP but not to B-TURP with regard to transfusion rate and clot retention [323].

180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications. Re-operation free survival during a 24 month follow-up was comparable between the TURP-arm and the 180-W XPS laser-arm [463]. In an RCT comparing the 120-W HPS laser with TURP, with a follow-up of 36 months, the re-operation rate was significantly higher after PVP (11% vs. 1.8%; p = 0.04) [464].

Based mostly on case series, the 80-,120- and 180-W Greenlight laser appears to be safe in high-risk patients undergoing anticoagulation treatment [469-472]; however, patients under anticoagulation therapy were either excluded from or represented a very small sample in currently available RCTs. In one study, anticoagulant patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [472]. In contrast, another retrospective study focusing on the 180-W LBO laser did not find any significant differences between patients receiving or not receiving anticoagulants [473]. A retrospective study of a mixed cohort of patients, treated with 80-W KTP PVP and 120-W LBO HPS, revealed that delayed gross haematuria was common in patients (33.8%) during an average follow-up of 33 months [474]. A retrospective review of a database of patients undergoing 180-W PVP, without interruption of anticoagulation therapy, had a 30.5% rate of peri-operative adverse events with a significant occurrence of high grade Clavien Dindo events [475].

Safety in patients with urinary retention, impaired detrusor contractility, elderly patients or prostates > 80 mL was shown in various prospective short-term non-randomised trials. No RCT including prostates > 100 mL has been reported; therefore, comparison of retreatment rates between prostate volumes of different sizes is not possible [476-478].

A meta-analysis of five RCTs comparing collectively all three “Greenlight” lasers with TURP detected no difference in retrograde ejaculation rates [398]. An RCT with twelve months follow-up reported a retrograde ejaculation rate of 49.9% following PVP with an 80-W laser vs. 56.7% for TURP, there was no impact on erectile function in either arm of the trial [479]. Additional studies have also reported no difference between OP/TURP and Greenlight PVP for erectile function [480, 481]. However, IIEF-5 scores were significantly decreased at six-, twelve-, and 24- months in patients with pre-operative IIEF-5 greater than nineteen [482].

No significant difference with respect to peri- and post-operative complications was reported in an RCT comparing B-TUVP and PVP with the 180-W XPS Laser. Redo TURP for recurrent adenoma was required in 9.8% (B-TUVP) and 1.7% (PVP) of the patients during 24-months follow-up, respectively [468].

Practical considerations: The 180-W XPS represents the current standard of generators for PVP; however, the number and quality of supporting publications are low, especially for large glands (> 100 mL), with no long-term follow-up.

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 80-W KTP and the 120-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay are in favour of PVP, whereas operation time and risk of re-operation are in favour of TURP. Short-term results for the 80-W KTP laser and mid-term results for the 120-W LBO laser were comparable to TURP.	1a
Laser vaporisation of the prostate using the 180-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay were in favour of PVP, whereas operation time was in favour of TURP. Short- to mid-term results are comparable to TURP.	1b
Laser vaporisation of the prostate using the 80-W KTP and 120-W LBO lasers seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy.	2
Laser vaporisation of the prostate using the 180-W LBO laser seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy; however, the level of evidence available is low.	3

Recommendations	**Strength rating**
Offer 80-W 532-nm Potassium-Titanyl-Phosphate (KTP) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate (TURP).	Strong
Offer 120-W 532-nm Lithium Borat (LBO) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer 180-W 532-nm LBO laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong

Offer laser vaporisation of the prostate using 80-W KTP, 120- or 180-W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80 mL.	Weak

5.3.3.3 Vaporisation techniques under investigation

5.3.3.3.1 Diode laser vaporisation of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 980 nm are marketed for vaporisation; however, only a few have been evaluated in clinical trials [333].

Efficacy: Two RCTs for 120-W 980 nm diode laser vaporisation vs. M-TURP are available [483, 484]. The first RCT with 24-month follow-up reported equal symptomatic and clinical parameters at one and six months. However, at twelve- and 24-months the results were significantly in favour of TURP, repeat TURP was more frequent in the diode laser group [483]. The second RCT reported equivocal results for both interventions at three-month follow-up [484].

Tolerability and safety: Published studies on 980 nm diode laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [485, 486]. In a number of studies, a high rate of post-operative dysuria was reported [483, 485-487]. A meta-analysis comparing diode laser vaporisation vs. M-TURP reported shorter catheterisation time and lower transfusion rates for diode laser vaporisation [323]. In an RCT reflecting on peri-operative and post-operative complications no significant differences were demonstrated for clot retention, AUR after catheter removal, UUI and UTI [483]. Moreover, for late complications no significant differences could be demonstrated for re-operation rate, urethral stricture, bladder neck sclerosis, *de novo* sexual dysfunction and mean time of dysuria [483].

Fibre modifications can potentially reduce surgical time [488]. Early publications on diode vaporisation reported high re-operation rates (8-33%) and persisting SUI (9.1%) [483, 485-487].

Practical considerations: Diode laser vaporisation leads to similar improvements in clinical and symptomatic parameters during short-term follow-up and provides good haemostatic properties. Based on the limited number of mainly low quality RCTs, and controversial data on the retreatment rate, results for diode laser vaporisation should be evaluated in further higher quality RCTs.

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 120-W 980 nm diode laser demonstrated high intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters like catheterisation time and hospital stay were in favour of diode lasers. Evidence is limited by the number and quality of the available studies.	1b
In a number of studies severe post-operative complications such as severe storage symptoms, and persisting incontinence occurred with laser vaporisation of the prostate using the 120-W 980 nm diode laser.	3
Laser vaporisation using the 120-W 980 nm diode laser seems to be safe with regard to haemostasis in patients receiving anticoagulant therapy.	3

5.3.4 ***Alternative ablative techniques***

5.3.4.1 Aquablation – image guided robotic waterjet ablation: AquaBeam

Mechanism of action: AquaBeam uses the principle of hydro-dissection to ablate prostatic parenchyma while sparing collagenous structures like blood vessels and the surgical capsule. A targeted high velocity saline stream ablates prostatic tissue without the generation of thermal energy under real-time transrectal ultrasound guidance; therefore, it is truly a robotic operation. After completion of ablation haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary [489].

Efficacy: In a double-blind, multicentre, prospective RCT 181 patients were randomised to TURP or Aquablation [490, 491]. Mean total operative time was similar for Aquablation and TURP (33 vs. 36 minutes), but resection time was significantly lower for Aquablation (4 vs. 27 minutes). At six months patients treated with Aquablation and TURP experienced large IPSS improvements (-16.9 and -15.1, respectively). The study non-inferiority hypothesis was satisfied. Larger prostates (50-80 mL) demonstrated a more pronounced benefit. At one year follow-up, mean IPSS reduction was 15.1 with a mean percent reduction in IPSS score of 67% for both groups. Ninety three percent and 86.7% of patients had improvements of at least five points from baseline, respectively. No significant difference in improvement of IPSS, QoL, Q_{max} and reduction of PVR was

reported between the groups. One TURP subject (1.5%) and three Aquablation subjects (2.6%) underwent re-TURP within one year of the study procedure [492].

At two years, improvements in IPSS and flow rate were maintained in both groups [493]. Surgical retreatment rates after twelve months for Aquablation were 1.7% and 0% for TURP. Over three years, mean IPSS improvements were 14.4 and 13.9 points in the Aquablation and TURP groups, respectively. Similarly, three-year improvements in Q_{max} were 11.6 and 8.2 cc/sec. There were no surgical retreatments for BPH beyond twenty months, for either Aquablation or TURP [494]. Over three years, surgical retreatments were 4.3% and 1.5% respectively. A limitation of RCTs is whether they are generalisable; however, a cohort study reported similar results in their first 118 consecutive patients [495].

A subgroup analysis of the WATER study [490] reported that in men with larger more complex prostates, Aquablation was associated with both superior symptom improvement and a better safety profile with less post-operative anejaculation [496].

In a cohort study of 101 men (WATER II) with a prostate volume between 80-150 mL, mean IPSS improved from 23.2 at baseline to 5.9 at six months. Improvement in IPSS, QoL, Q_{max} and reduction of PVR were also significant at six months [497]. At twelve months, significant improvements were seen in Q_{max} (increase of 12.5 cc/sec) and PVR (drop of 171 cc) in those with PVR > 100 at baseline). No patient underwent a repeat procedure for BPH symptoms [498]. In a comparison of the WATER (RCT: prostates 30-80 cc) and WATER II (cohort study; > 80 cc) at two years, the improvements were maintained in both IPSS and flow rates. At two years, the surgical retreatment rate was 4% in WATER and 2% in WATER II [499].

Another RCT comparing Aquablation with TURP performed urodynamic studies on 66 patients at six months follow-up and reported significant changes in pdetQ_{max} (reductions of 35 and 34 cm H_20, respectively) and large improvements in BOO index in both groups [500].

Tolerability and safety: An RCT has shown that fewer men in the Aquablation group had a persistent Clavien-Dindo grade 1 or 2 or higher adverse event compared to TURP (26% vs. 42%) at three months following treatment. Among sexually active men the rate of anejaculation was lower in those treated with Aquablation compared to TURP (10% vs. 36%, respectively). There were no procedure-related adverse events after six months [492]. Maintenance of antegrade ejaculation was slightly lower in WATER II 81% compared to 90% in the smaller prostates of WATER I [501].

In patients with a prostate volume between 80-150 mL, bleeding related events were observed in fourteen patients (13.9%) of which eight (7.9%) occurred prior to discharge and six (5.9%) occurred within one month of discharge. Blood transfusions were required in eight (7.9%) patients, return to the theatre for fulguration in three (3.0%) patients, and both transfusion and fulguration in two patients (2.0%) [497]. In WATER II there was a 2% incontinence rate at twelve months, and ten patients did require a transfusion post-operatively while five required take-back fulgurations [498].

In a SR of seven patient groups involving 446 patients treated by aquablation, although there was a significant haemoglobin drop (2.06 g/dL), it did not translate into increased transfusion rates. Aquablation achieves overall lower rates of adverse events. In the first three months of the WATER RCT Clavien Dindo 2-5 events occurred in 19% for aquablation and 29% for TURP (NS). Between three and twelve months they occurred in 5.3% and 10.7% respectively and there was no statistically significant difference again between the one- and two-year follow-up [502].

Practical considerations: During mid-term follow-up, aquablation provides non-inferior functional outcomes compared to TURP in patients with LUTS and a prostate volume between 30-80 mL. Longer term follow-up is necessary to assess the clinical value of aquablation.

Summary of evidence	**LE**
Aquablation appears to be as effective as TURP both subjectively and objectively; however, there are still some concerns about the best methods of achieving post-treatment haemostasis.	1b

Recommendations	**Strength rating**
Offer Aquablation* to patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL as an alternative to TURP.	Weak
Inform patients about the risk of bleeding and the lack of long-term follow-up data.	Strong

** Aquablation remains under investigation*

5.3.4.2 Prostatic artery embolisation

Mechanism of action: Prostatic artery embolisation (PAE) can be performed as a day procedure under local anaesthesia with access through the femoral or radial arteries. Digital subtraction angiography displays arterial anatomy, and the appropriate prostatic arterial supply is selectively embolised to effect stasis in treated prostatic vessels. Different techniques have been used for PAE. Atherosclerosis, excessive tortuosity of the arterial supply and the presence of adverse collaterals are anatomical obstacles for the technical approach. Cone beam computed tomography and contrast enhanced MR angiography can help identify prostatic arteries and prevent off-target embolisation particularly in patients with challenging anatomical configurations [503, 504].

Efficacy: Superior efficacy of PAE compared with a sham procedure was found in a six-month randomised, single-blind, sham-controlled trial in 80 patients with severe LUTS, refractory to medical treatment. The decrease in IPSS was significant at six months, 5.03 +/- 8.13 in the sham group and 17.1 +/- 7.25 in the PAE group [505].

In two earlier RCTs conducted for direct comparison of PAE with TURP [506, 507], both studies observed significant treatment outcomes for both procedures as compared to baseline values, but TURP was superior when considering urodynamic parameters such as Q_{max} and PVR. Improvement of LUTS as determined by IPSS and QoL was slightly more pronounced after TURP, and reduction of prostate volume was significantly more efficient after TURP than PAE.

An RCT comparing PAE with TURP in 99 patients showed a mean reduction in IPSS from baseline to twelve weeks of –9.23 points after PAE and –10.77 points after TURP. At twelve weeks, PAE was less effective than TURP regarding improvements in Q_{max} (5.19 mL/s vs. 15.34 mL/s), PVR (–86.36 mL vs. –199.98 mL), prostate volume (–12.17 mL vs. –30.27 mL), and significant de-obstructive effectiveness according to pressure flow studies (56% vs. 93% shift towards less obstructive category) [503]. An RCT of 60 patients randomised into three equal arms of M-TURP, B-TURP, and PAE followed up at six months concluded that improvement in IPSS score, and Q_{max}, but not in PVR were statistically significantly better for M-TURP and B-TURP vs. PAE [508]. A two-year follow up of this RCT showed no significant difference in IPSS improvement (9.21 points for PAE and 12.09 points for TURP) but TURP was superior for flow rate, prostate volume and PVR improvement. Twenty one percent of patients who initially had PAE underwent TURP within two years. There were less complications for PAE [509].

A SR and meta-analysis including the three above mentioned RCTs and two non-RCTs comparative studies (n = 708 patients), showed that TURP achieved a significantly higher mean post-operative difference for IPSS and IPSS-QoL, 3.80 and 0.73 points, respectively compared to PAE [510]. All of the functional outcomes assessed were significantly superior after TURP: 3.62 mL/s for Q_{max}, 11.51 mL for prostate volume, 11.86 mL for PVR, and 1.02 ng/mL for PSA [510]. A meta-analysis of four RCTs concluded that TURP is associated with significantly higher improvements in Q_{max} [511]. The mean differences in IPSS, QoL score and PVR were not significantly different between TURP and PAE [511].

A recent SR and Meta-analysis including six studies with 598 patients showed that TURP resulted in significantly greater improvement in Q_{max}, prostate volume, and PSA compared to PAE [511]. However, there was no significant difference between PAE and TURP in IPSS improvement, IPSS QoL, IIEF and PVR. PAE was associated with significantly fewer adverse events (39.0% vs. 77.7%) and shorter hospitalisation times (mean difference = -1.94 days), but longer procedural times (mean difference = 51.43 min) [511].

Another SR and meta-analysis of ten RCTs (one vs. sham, five vs. TURP and four exploring variations in PAE technique) confirmed that PAE is non-inferior to TURP in improving patient reported outcome measures (PROMs), though TURP is superior to PAE for most objective outcomes [512].

In a single centre retrospective analysis of 75 PAE patients over a three-year period, PAE was shown to be a safe, effective, and durable treatment option for non-index patients with urinary retention (87% catheter free) or gross haematuria (resolved 87.5%) [513].

Tolerability and safety: In a SR of comparative studies PAE resulted in significantly more adverse events than TURP/OP (41.6% vs. 30.4%). The frequency of AUR after the procedures was significantly higher in the PAE group (9.4% vs. 2.0%) [514].

Another RCT however, reported significantly fewer adverse events occurred after PAE than after TURP (36 vs. 70 events). For secondary outcomes, PAE showed favourable results in terms of blood loss [503]. A RCT of 60 patients randomised into three equal arms of M-TURP, B-TURP, and PAE followed up at six months concluded that operative time was significantly longer for PAE (89 min for PAE vs. 59 min and 68 min for M-TURP and B-TURP) [508]. Catheter was removed on the third and fifth day in the TURP and PAE arms, respectively. No significant haemoglobin drop was detected (no need for blood transfusions) among arms. One patient developed TUR syndrome in the M-TURP arm; two patients from the PAE group developed AUR after catheter removal and four patients from the PAE group developed postembolisation syndrome [508].

A subsequent SR and meta-analysis of four studies (506 patients) comparing PAE and TURP found no significant difference in the post-operative complication rate between TURP and PAE [515]. A SR of 708 patients reported fewer side effects than established surgical procedures [510]. A meta-analysis of four RCTs concluded that PAE was associated with significantly shorter hospitalisation time, longer procedural time, fewer total side effects but similar rates of severe side effects [511]. The mean differences in IIEF-5 score were not significantly different between TURP and PAE [511]. Another meta-analysis of two RCTs detected no difference in retrograde ejaculation rates [398]. Post-operative erectile function measured by IIEF-5 was in favour of PAE with mean difference in change of 2.56 points. In another updated meta-analysis PAE was associated with lower sexual dysfunction than TURP (OR 0.24) [516].

Concerns still exist about non-target embolisation, reported in earlier studies [517]; however, more recent studies report less incidents [510, 518].

A SR of 22 studies reporting radiation exposure during PAE, with a twenty-fold range of exposures, estimated that the median risk for a 66-year-old patient of a cancer related death was 0.117%, equivalent to a reduced life expectancy of 5.4 days. Radiation exposure therefore should be part of the counselling for patients considered for PAE. These data suggest there is potential for significant radiation reduction in some centres using appropriate protocols [519].

For secondary outcomes, procedural time was shorter for TURP, but in PAE patients, bladder catheter indwelling time, and duration of hospital stay were significantly shorter [462].

Practical considerations: A multidisciplinary team approach of urologists and radiologists is mandatory and patient selection should be done by urologists and interventional radiologists. The investigation of patients with LUTS to indicate suitability for invasive techniques should be performed by urologists only. This technically demanding procedure should only be done by an interventional radiologist with specific mentored training and expertise in PAE [520]. There are data suggesting that larger prostates have a higher chance of a superior outcome with PAE in post hoc analysis of RCTs, but larger trials are required to clarify the most suitable patients for PAE [497, 521].

Further data with medium- and long-term follow-up are still required and comparison with other minimally invasive techniques would be valuable. However, current evidence of safety and efficacy of PAE appears adequate to support the use of this procedure for men with moderate-to-severe LUTS provided proper arrangements for consent and audit are in place; therefore, a recommendation has been given, but PAE remains under investigation.

Summary of evidence	**LE**
Prostatic artery embolisation is less effective than TURP at improving symptoms and urodynamic parameters such as flow rate.	1a
Procedural time is longer for PAE compared to TURP, but blood loss, catheterisation and hospitalisation time are in favour of PAE.	1b

Recommendations	**Strength rating**
Offer prostatic artery embolisation (PAE)* to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal outcomes compared with transurethral resection of the prostate.	Weak
Perform PAE only in units where the work up and follow-up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients.	Strong

** PAE remains under investigation*

5.3.4.3 Alternative ablative techniques under investigation

5.3.4.3.1 Convective water vapour energy (WAVE) ablation: The Rezum system

Mechanism of action: The Rezum system uses radiofrequency power to create thermal energy in the form of water vapour, which in turn deposits the stored thermal energy when the steam phase shifts to the liquid phase upon cell contact. The steam disperses through the tissue interstices and releases stored thermal energy onto prostatic tissue effecting cell necrosis. The procedure can be performed in an office-based setting. Usually, one to three injections are needed for each lateral lobe and one to two injections may be delivered into the median lobe.

Efficacy: In a multicentre RCT, 197 men were enrolled and randomised in a 2:1 ratio to treatment with water vapour energy ablation or sham treatment [522]. At three months relief of symptoms, measured by a change in

IPSS and Q_{max} were significantly improved and maintained compared to the sham arm, although only the active treatment arm was followed up to twelve months. No relevant impact was observed on PVR. Quality of life outcome was significantly improved with a meaningful treatment response of 52% at twelve months. Further validated objective outcome measures such as BPH impact index (BPHII), Overactive Bladder Questionnaire Short Form for OAB bother, and impact on QoL and ICS Male Item Short Form Survey for male incontinence demonstrated improvement of symptoms at three months follow-up with sustained efficacy throughout the study period of twelve months. The reported two-year results in the Rezum cohort arm of the same study and the recently reported four-year results confirmed durability of the positive clinical outcome after convective water vapour energy ablation [523, 524]. Surgical retreatment rate was 4.4% over four years [524]. A Cochrane review found no studies comparing convective radiofrequency water vapour thermal therapy to any other active treatment form, such as TURP [525].

Tolerability and safety: Safety profile was favourable with adverse events documented to be mild-to-moderate and resolving rapidly. Preservation of erectile and ejaculatory function after convective water vapour thermal therapy was demonstrated utilising validated outcome instruments such as IIEF and Male Sexual Health Questionnaire-Ejaculation Disorder Questionnaire [522].

Practical considerations: There are two SRs of the Rezum cohort studies. One concludes that Rezum provides improvement in BPH symptoms that exceeds established minimal clinically important difference thresholds, preserves sexual function, and is associated with low surgical retreatment rates over four years. Therefore, suggesting that it may be a valuable addition to the urological armamentarium to treat LUTS in men with BPH [526]. The other, a Cochrane review reported that the certainty of evidence ranged from moderate to very low, with study limitations and imprecision being the most common reasons for down-grading of the evidence [525]. Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapour energy treatment.

*5.3.5 **Non-ablative techniques***

5.3.5.1 Prostatic urethral lift

Mechanism of action: The prostatic urethral lift (PUL) represents a novel minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance (Urolift®) resulting in an opening of the prostatic urethra leaving a continuous anterior channel through the prostatic fossa extending from the bladder neck to the verumontanum.

Efficacy: In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%) [527-532]. Prostatic urethral lift was initially evaluated vs. sham in a multicentre study with one [529] three [533] and five [534] years follow-up of the treated cohort. The primary endpoint was met at three months with a 50% reduction in IPSS. In addition, Q_{max} increased significantly from 8.1 to 12.4 mL/s compared to baseline at three months and this result was confirmed at twelve months. The difference in clinical response for Q_{max} between both groups was of statistical significance. A relevant benefit with regard to PVR was not demonstrated compared to baseline or sham. At three years, average improvements from baseline were significant for total IPSS, QoL, Q_{max} and individual IPSS symptoms. There was no, *de novo*, sustained ejaculatory or erectile dysfunction events and all sexual function assessments showed average stability or improvement after PUL. Improvements in IPSS, QoL, BPHII, and Q_{max} were durable throughout the five years with improvement rates of 36%, 50%, 52%, and 44%, respectively. The re-treatment rate was 13.6% over five years. Adverse events were mild to moderate and transient. Sexual function was stable over five years with no, *de novo*, sustained erectile, or ejaculatory dysfunction.

Another RCT of 80 patients was conducted in three European countries, comparing PUL to TURP. At twelve months, IPSS improvement was -11.4 for PUL and -15.4 for TURP. There was no retrograde ejaculation among PUL patients with 40% in the TURP patients. Surgical recovery was measured using a validated instrument and confirmed that recovery from PUL is more rapid and more extensive in the first three to six months [535]. However, TURP resulted in much greater improvements in Q_{max} after twelve months compared to PUL. At 24 months, significant improvements in IPSS, IPSS QoL, BPHII, and Q_{max} were observed in both arms. Change in IPSS and Q_{max} in the TURP arm were superior to the PUL arm [536]. Improvements in QoL and BPHII score were not statistically different between the study arms. Prostatic urethral lift resulted in superior quality of recovery and ejaculatory function preservation. Ejaculatory function and bother scores did not change significantly in either treatment arm.

In a meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS, Q_{max}, and QoL [532]. Sexual function was preserved with a small improvement estimated at twelve months.

A retrospective observational study of 1,413 consecutive patients from North America and Australia split patients into those still voiding (Group A) and those in retention (Group B). The results from Group A were comparable to the results from the clinical trials and of the 165 patients in Group B, 69% were catheter free after five days, 83% after one month and 89% by study end [537].

A Cochrane review of the sham RCT and the RCT against TURP concluded that PUL appears less effective than TURP in improving urological symptoms in both the short- and long term, while QoL outcomes may be similar. The effect on erectile function appears similar but ejaculatory function may be better with PUL [538].

A SR of surgical re-interventions of eleven studies (2,016 patients), among which TURP/laser (51.0%), repeat PUL (32.7%) and device explant (19.6%) were most common, revealed an annual rate of surgical re-intervention of 6.0% per year (95% CI: 3.0-8.9) [539].

Tolerability and safety: The most common complications reported post-operatively included haematuria (16-63%), dysuria (25-58%), pelvic pain (5-17.9%), urgency (7.1-10%), transient incontinence (3.6-16%), and UTI (2.9-11%) [529, 532-534]. Most symptoms were mild-to-moderate in severity and resolved within two to four weeks after the procedure.

Prostatic urethral lift seems to have no significant impact on sexual function. Evaluation of sexual function as measured by IIEF-5, Male Sexual Health Questionnaire-Ejaculatory Dysfunction, and Male Sexual Health Questionnaire-Bother in patients undergoing PUL showed that erectile and ejaculatory function were preserved [527-531]. A SR and meta-analysis found that sexual function remained stable or improved slightly during the 24-month follow-up period [512].

Practical considerations: There are only limited data on treating patients with an obstructed/protruding middle lobe [540]. It appears that they can be effectively treated with a variation in the standard technique, but further data are needed [540]. The effectiveness in large prostate glands has not been shown yet. Long-term studies are needed to evaluate the duration of the effect in comparison to other techniques.

Summary of evidence	**LE**
Prostatic urethral lift improves IPSS, Q_{max} and QoL; however, these improvements are inferior to TURP at 24 months.	1b
Prostatic urethral lift has a low incidence of sexual side effects.	1b
Patients should be informed that long-term effects, including the risk of retreatment, have not been evaluated.	4

Recommendation	**Strength rating**
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe.	Strong

5.3.5.2 Intra-prostatic injections

Mechanism of action: Various substances have been injected directly into the prostate in order to improve LUTS, these include Botulinum toxin-A (BoNT-A), fexapotide triflutate (NX-1207) and PRX302. The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [541]. The detailed mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data suggests apoptosis-induced atrophy of the prostate with both drugs [541].

Efficacy: Results from clinical trials have shown only modest clinical benefits, that do not seem to be superior to placebo, for BoNT-A [542, 543]. A SR and meta-analysis showed no differences in efficacy compared with placebo and concluded that there is no evidence of clinical benefit in medical practice [544]. The positive results from Phase II-studies have not been confirmed in Phase III-trials for PRX302 [545, 546]. NX-1207 was evaluated in two multicentre placebo controlled double-blind randomised parallel group trials including a total of 995 patients with a mean follow-up of 3.6 years, IPSS change from baseline was significantly higher and AUR rate was significantly reduced in the treatment arm. The authors concluded that NX-1207 is an effective transrectal injectable for long-term treatment for LUTS and that treated patients have reduced need for further intervention [547].

Safety: Studies including safety assessments have reported only a few mild and self-limiting adverse events for all injectable drugs [541]. A SR and meta-analysis showed low incident rates of procedure-related adverse

events [544]. Two multicentre placebo controlled double-blind randomised parallel group trials with long-term follow-up evaluating NX-1207 detected no significant safety differences between the study arms [547].

Practical considerations: Although experimental evidence for compounds such as PRX302 were promising for their transition to clinical use positive results from Phase II-studies have not been confirmed in Phase III-trials. Nevertheless, an RCT evaluating transperineal intraprostatic BoNT-A injection vs. TURP concluded that IPSS significantly decreased in all patients, with a non-significant difference between the arms and that the BoNT-A injection significantly maintained erectile function compared to TURP at twelve months [548]. More high-quality evidence against reference techniques is needed.

Summary of evidence	**LE**
Results from clinical trials have shown no clinical benefits for BoNT-A compared to placebo for the management of LUTS due to BPO.	1a
Results from clinical trials have shown clinical benefits for NX-1207 compared to placebo for the management of LUTS due to BPO.	1b

Recommendation	**Strength rating**
Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS.	Strong

5.3.5.3 Non-ablative techniques under investigation

5.3.5.3.1 (i)TIND

Mechanism of action: The iTIND is a device designed to remodel the bladder neck and the prostatic urethra and is composed of three elongated struts and an anchoring leaflet, all made of nitinol. Under direct visualisation the iTIND is deployed inside the prostate in expanded configuration. The intended mode of action is to compress obstructive tissue by the expanded device, thereby exerting radial force leading to ischaemic necrosis in defined areas of interest. The iTIND is left in position for five days. The resulting incisions may be similar to a Turner Warwick incision. In an outpatient setting the device is removed by standard urethroscopy.

Efficacy: A single-arm, prospective study of 32 patients with a follow-up of three years was conducted to evaluate feasibility and safety of the procedure [549]. The change from baseline in IPSS, QoL score and Q_{max} was significant at every follow-up time point [550].

In a prospective multicentre study, 81 patients were enrolled and treated with a second generation iTIND device. Mean Q_{max} at one month increased from 7.3 to 11.2 (5.7) ml/s and was 14.7 ml/s at twelve months. The IPSS decreased from 22.5 to 11.7 after one month and to 8.8 at twelve months. In parallel, the mean IPSS QoL score drop reached 1.6 by the end of the study. During the twelve-month period, two patients required medical therapy, two patients required TURP, and ten patients were lost to follow-up [551].

In a multicenter RCT, 175 men were randomised 2:1 between iTIND and sham procedures. Patients were assessed at baseline, 45 days, three, and twelve months postoperatively. Unblinding occurred at three months. A total of 78.6% of patients in the iTIND arm showed a reduction of ≥ 3 points in IPSS, vs. 60% of patients in the control arm at three months. At twelve months, compared to baseline, the iTIND group reported a mean 9.25 decrease in IPSS, a 3.52mL/s increase in peak urinary flow rate and a 1.9-point reduction in QoL. There was a comparable loss of follow-up from baseline groups to three months of 29% of patients in the iTIND arm, and 30% of patients in the sham arm [552].

Tolerability and safety: The device have been reported as well tolerated by all patients. Four early complications (12.5%) were recorded, including one case of urinary retention (3.1%), one case of transient incontinence due to device displacement (3.1%), and two cases of infection (6.2%). No further complications were recorded during the 36-month follow-up period.

Using the second-generation device none of the 61 sexually active patients who completed the twelve-month follow-up period reported sexual or ejaculatory dysfunction compared to baseline[551].

In the RCT against sham study adverse events were typically mild and transient, most were Clavien-Dindo grade 1 or 2 with 38.1% in the iTIND arm and 17.5% in the control arm. No new ejaculatory or erectile dysfunction occurred [552].

Practical considerations: Randomised controlled trials comparing iTIND to a reference technique are ongoing.

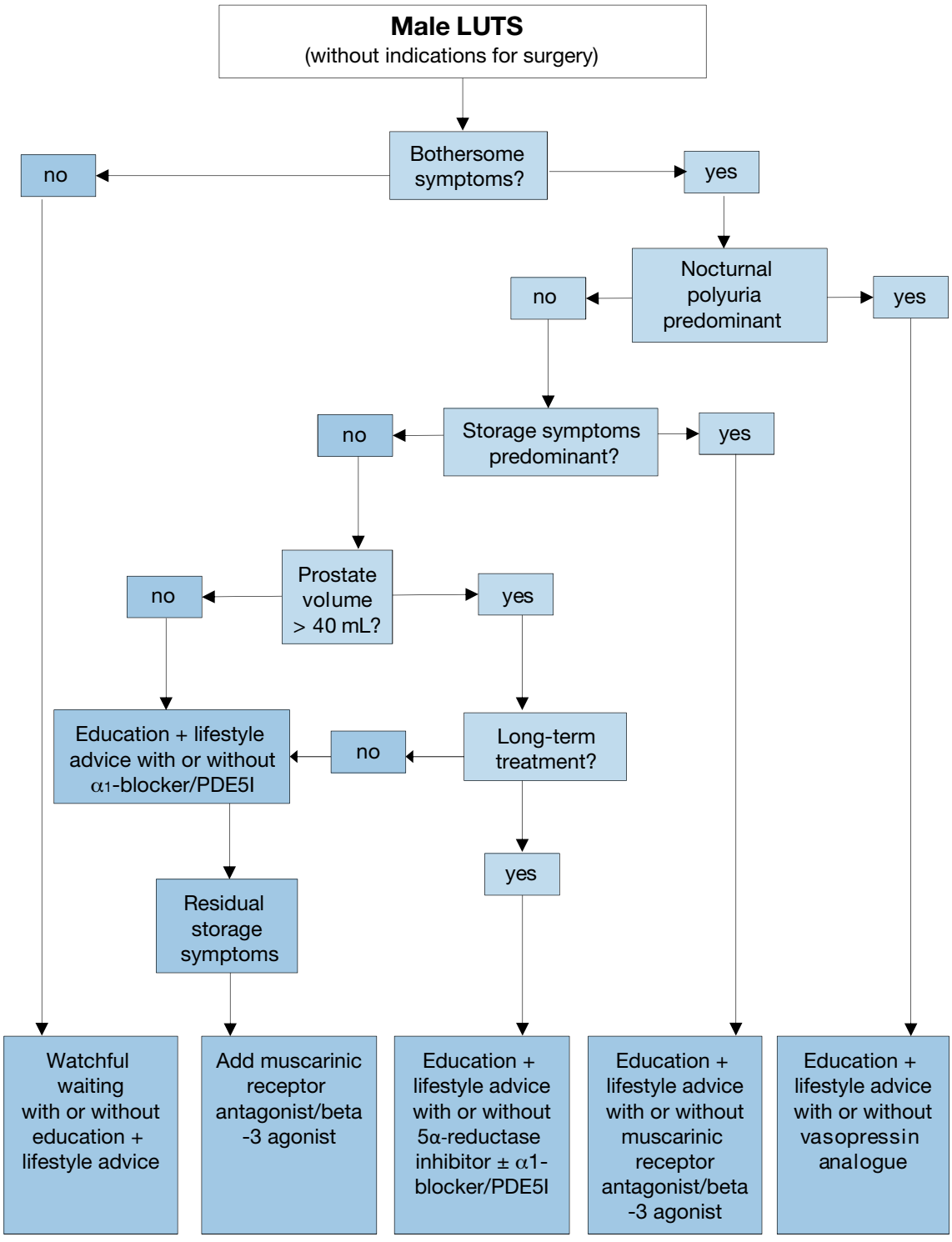
5.4 Patient selection

The choice of treatment depends on the assessed findings of patient evaluation, ability of the treatment to change the findings, treatment preferences of the individual patient, and the expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression.

Behavioural modifications, with or without medical treatments, are usually the first choice of therapy. Figure 3 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles. Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery).

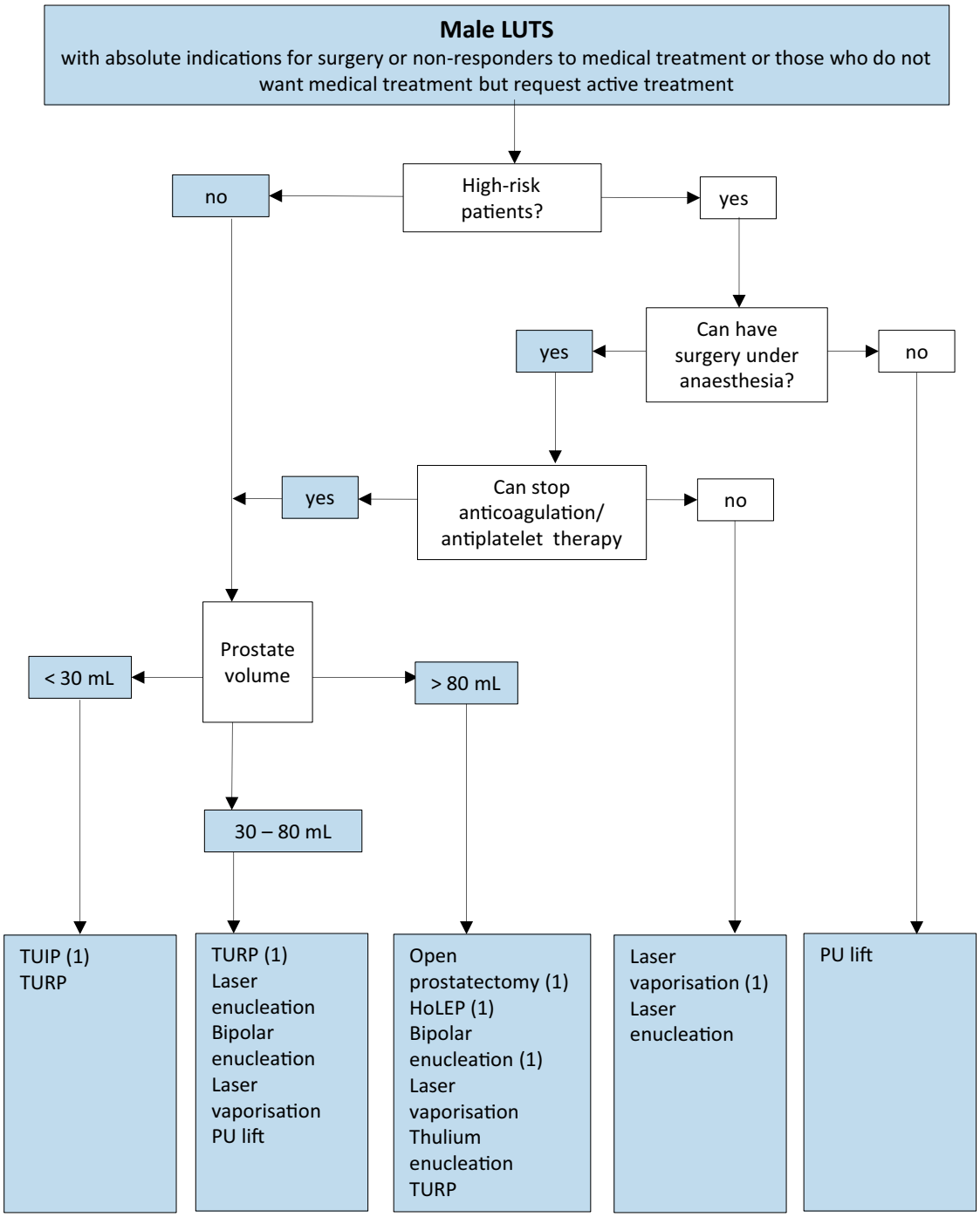
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches according to evidence-based medicine and the patient's profile is provided in Figure 4.

Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options
Treatment decisions depend on results assessed during initial evaluation.
Note that patients' preferences may result in different treatment decisions.



PDE5I = phosphodiesterase type 5 inhibitors.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart is stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size.



(1) Current standard/first choice. The alternative treatments are presented in alphabetical order. Laser vaporisation includes GreenLight, thulium, and diode laser vaporisation. Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; PU = prostatic urethral; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

5.5 Management of Nocturia in men with lower urinary tract symptoms

The following section reports a SR of therapy for the management of nocturia in men with LUTS. It also emphasises the need to consider the wide range of possible causes of nocturia [553].

Nocturia has been defined as the complaint of waking at night to void [6]. The ICS Standardisation Steering Committee has introduced the concept of *main sleep period*, defined as "the period from the time of

falling asleep to the time of intending to rise for the next "day" [554].

Nocturia reflects the relationship between the amount of urine produced while asleep, and the ability of the bladder to store the urine received. Nocturia can occur as part of lower urinary tract dysfunction (LUTD), such as OAB and chronic pelvic pain syndrome. Nocturia can also occur in association with other forms of LUTD, such as BOO, but here it is debated whether the link is one of causation or simply the co-existence of two common conditions. Crucially, nocturia may have behavioural, sleep disturbance (primary or secondary) or systemic causes unrelated to LUTD (Table 2). Differing causes often co-exist and each has to be considered in all cases. Only where LUTD is contributory should nocturia be termed a LUTS.

Table 2: Categories of nocturia

CATEGORY	Disproportionate urine production (at all times, or during sleep)	Low volume of each void (at all times, or overnight)
Behavioural	Inappropriate fluid intake	"Bladder awareness" due to secondary sleep disturbance
Systemic	Water, salt and metabolite output	
Sleep disorder	Variable water and salt output	"Bladder awareness" due to primary sleep disturbance
LUTD		Impaired storage function and increased filling sensation

*5.5.1 **Diagnostic assessment***

Evaluation is outlined in Figure 5;

1. Evaluate for LUTD according to the relevant guidelines. The severity and bother of individual LUTS should be identified with a symptom score, supplemented by directed questioning if needed. A validated bladder diary is mandatory.
2. Review whether behavioural factors affecting fluid balance and sleep are contributing.
3. Review of medical history and medications, including directed evaluation for key conditions, such as renal failure, diabetes mellitus, cardiac failure, and obstructive sleep apnoea. If systemic factors or sleep disorders are potentially important, consider involving appropriate medical expertise (see Figure 6). This is appropriate where a known condition is sub optimally managed, or symptoms and signs suggest an undiagnosed condition.

*5.5.2 **Medical conditions and sleep disorders Shared Care Pathway***

Causative categories for nocturia comprise [555]:

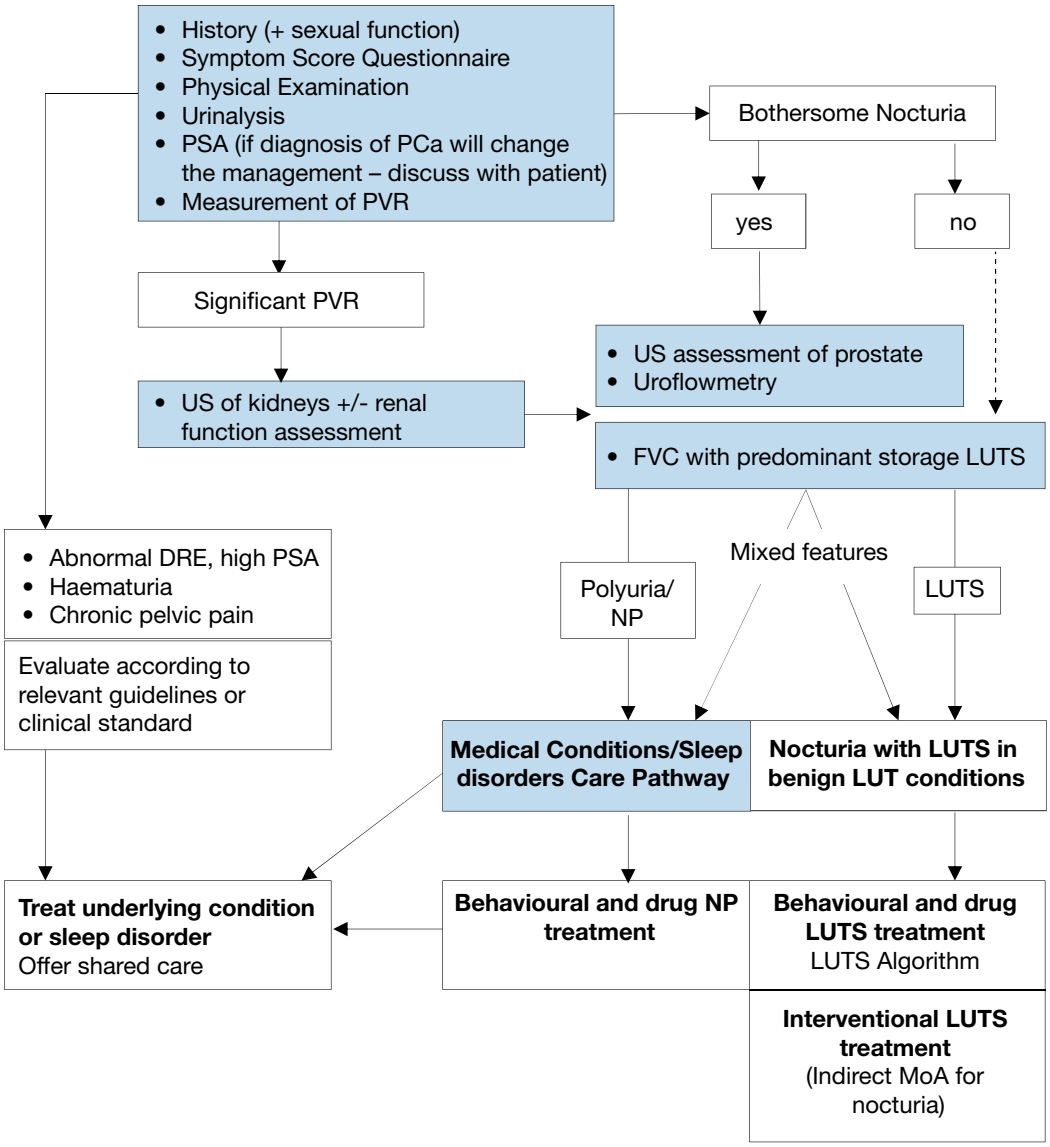
1. bladder storage problems;
2. 24-hour polyuria (> 40 mL/kg urine output over a 24-hour period);
3. nocturnal polyuria (NP; defined as excessive production of urine during the individual's main sleep period, i.e. nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [6]);
4. sleep disorders;
5. mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on the levels of free water, salt, other solutes, and plasma oncotic pressure; endocrine regulation e.g., by antidiuretic hormone; natriuretic peptides; cardiovascular and autonomic control; renal function; neurological regulation, e.g., circadian regulation of the pineal gland, and renal innervation. As nocturia is commonly referred to the specialty without full insight into cause, the urologist must review the likely mechanisms underlying a presentation with nocturia and instigate review by relevant specialties accordingly. Thus, the managing urologist needs to evaluate nocturia patients in a context where additional medical expertise is available (Table 3). They should not proceed along any LUTD management pathway unless a causative link with LUTD is justifiably suspected, and systemic or sleep abnormalities have been considered.

In patients with non-bothersome nocturia, the medical evaluation (history and physical examination) should consider the possibility of early stages of systemic disease, and whether there is possibility of earlier diagnosis or therapy adjustment.

Some important potentially treatable non-urological causes of nocturia include obstructive sleep apnoea, congestive cardiac failure, poorly controlled diabetes mellitus and medications (e.g., diuretics, or lithium).

Figure 5. Evaluation of Nocturia in non-neurogenic Male LUTS.



Assessment must establish whether the patient has polyuria, LUTS, a sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment with a frequency volume chart (indicated by the dotted line) depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.
FVC = frequency volume chart; DRE = digital rectal examination; NP = nocturnal polyuria; MoA = mechanism of action; PVR = post-void residual; PSA = prostate-specific antigen; US = ultrasound.

Table 3: Shared care pathway for nocturia, highlighting the need to manage potentially complex patients using relevant expertise for the causative factors.

UROLOGICAL CONTRIBUTION	SHARED CARE	MEDICAL CONTRIBUTION
Diagnosis of LUTD • Urological/LUTS evaluation • Nocturia symptom scores • Bladder diary		**Diagnosis of conditions causing NP** • Evaluate patient's known conditions • Screening for sleep disorders • Screening for potential causes of polyuria*
Conservative management Behavioural therapy • Fluid/sleep habits advice • Drugs for storage LUTS • Drugs for voiding LUTS • ISC/catherisation • Increased exercise • Leg elevation • Weight loss Interventional therapy • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS	**Conservative management** • Antidiuretic • Diuretics • Drugs to aid sleep	**Management** • Initiation of therapy for new diagnosis • Optimised therapy of known conditions * Potential causes of polyuria NEPHROLOGICAL DISEASE • Tubular dysfunction • Global renal dysfunction CARDIOVASCULAR DISEASE • Cardiac disease • Vascular disease ENDOCRINE DISEASE • Diabetes insipidus/mellitus • Hormones affecting diuresis/natriuresis NEUROLOGICAL DISEASE • Pituitary and renal innervation • Autonomic dysfunction RESPIRATORY DISEASE • Obstructive sleep apnoea BIOCHEMICAL • Altered blood oncotic pressure

ISC = intermittent self catherisation

*5.5.3 **Treatment for Nocturia***

5.5.3.1 Antidiuretic therapy

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and control of urine production by binding to V2 receptors in the renal collecting ducts. Arginine vasopressin increases water re-absorption and urinary osmolality, so decreasing water excretion and total urine volume. Arginine vasopressin also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for treating nocturia/nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and no relevant V1 receptor affinity. It has been investigated for treating nocturia [556], with specific doses, titrated dosing, differing formulations, and options for route of administration. Most studies have short follow-up. Global interpretation of existing studies is difficult due to the limitations, imprecision, heterogeneity and inconsistencies of the studies.

A SR of randomised or quasi-randomised trials in men with nocturia found that desmopressin may decrease the number of nocturnal voids by -0.46 compared to placebo over short-term follow-up (up to three months); over intermediate-term follow-up (three to twelve months) there was a change of -0.85 in nocturnal voids in a substantial number of participants without increase in major adverse events [557].

Another SR of comparative trials of men with nocturia as the primary presentation and LUTS including nocturia or nocturnal polyuria found that antidiuretic therapy using dose titration was more effective than placebo in relation to nocturnal voiding frequency and duration of undisturbed sleep [553]. Adverse events include headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema, and nausea. Three studies evaluating titrated-dose desmopressin in which men were included, reported seven serious adverse events in 530 patients (1.3%), with one death. There were seventeen cases of hyponatraemia (3.2%) and seven of hypertension (1.3%). Headache was reported in 53 (10%) and nausea in fifteen (2.8%) [553]. Hyponatremia is the most important concern, especially in patients > 65 years of age, with potential life-threatening consequences. Baseline values of sodium over 130 mmol/L have been used as inclusion criteria in some research protocols. Assessment of sodium levels must be undertaken at baseline, after initiation of treatment or dose titration and during treatment. Desmopressin is not recommended in high-risk groups [553].

Desmopressin oral disintegrating tablets (ODT) have been studied separately in the sex-specific pivotal trials CS41 and CS40 in patients with nocturia [558, 559]. Almost 87% of included patients had nocturnal polyuria and approximately 48% of the patients were > 65 years. The co-primary endpoints in both trials were change in number of nocturia episodes per night from baseline and at least a 33% decrease in the mean number of nocturnal voids from baseline during three months of treatment. The mean change in nocturia episodes from baseline was greater with desmopressin ODT compared to placebo (difference: women = -0.3 [95% CI: -0.5 to -0.1]; men = -0.4 [95% CI: -0.6 to -0.2]). The 33% responder rate was also greater with desmopressin ODT compared to placebo (women: 78% vs. 62%; men: 67% vs. 50%).

Analysis of three published placebo-controlled trials of desmopressin ODT for nocturia showed that clinically significant hyponatraemia was more frequent in patients aged ≥ 65 years than in those aged < 65 years in all dosage groups, including those receiving the minimum effective dose for desmopressin (11% of men aged ≥ 65 years vs. 0% of men aged < 65 years receiving 50 mcg; 4% of women ≥ 65 aged years vs. 2% of women aged < 65 years receiving 25 mcg). Severe hyponatraemia, defined as ≤ 125 mmol/L serum sodium, was rare, affecting 22/1,431 (2%) patients overall [560].

Low dose desmopressin ODT has been approved in Europe, Canada and Australia for the treatment of nocturia with ≥ 2 episodes in gender-specific low doses 50 mcg for men and 25 mcg for women; however, it initially failed to receive FDA approval, with the FDA citing uncertain benefit relative to risks as the reason. Following resubmission to the FDA in June 2018 desmopressin acetate sublingual tablet, 50 mcg for men and 25 mcg for women, was approved for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void with a boxed warning for hyponatremia.

Desmopressin acetate nasal spray is a new low-dose formulation of desmopressin and differs from other types of desmopressin formulation due to its bioavailability and route of administration. Desmopressin acetate nasal spray has been investigated in two RCTs including men and women with nocturia (over two episodes per night) and a mean age of 66 years. The average benefit of treatment relative to placebo was statistically significant but low, -0.3 and -0.2 for the 1.5 mcg and 0.75 mcg doses of desmopressin acetate, respectively. The number of patients with a reduction of more than 50% of nocturia episodes was 48.5% and 37.9%, respectively compared with 30% in the placebo group [561]. The reported adverse event rate of the studies was rather low, and the risk of hyponatremia was 1.2% and 0.9% for desmopressin acetate 1.5 mcg and 0.75 mcg, respectively. Desmopressin acetate nasal spray was approved by the FDA in 2017 for the treatment of nocturia due to nocturnal polyuria, but it is not available in Europe.

Practical considerations: A complete medical assessment should be made, to exclude potentially non-urological underlying causes, e.g., sleep apnoea, before prescribing desmopressin in men with nocturia due to nocturnal polyuria. The optimal dose differs between patients, in men < 65 years desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased up to a dosage of 0.4 mg/day every week until maximum efficacy is reached. Desmopressin is taken once daily before sleeping. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. Low dose desmopressin may be prescribed in patients > 65 years. In men ≥ 65 years or older, low dose desmopressin should not be used if the serum sodium concentration is below normal: all patients should be monitored for hyponatremia. Urologists should be cautious when prescribing low-dose desmopressin in patients under-represented in trials (e.g., patients > 75 years) who may have an increased risk of hyponatremia.

5.5.3.2 Medications to treat LUTD

Where LUTD is diagnosed and considered causative of nocturia, relevant medications for storage (and voiding) LUTS may be considered. Applicable medications include; selective α1-adrenergic antagonists [562], antimuscarinics [563-565], 5-ARIs [566] and PDE5Is [567]. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia [553]. Data on OAB medications (antimuscarinics, beta-3 agonist) generally had a female-predominant population. No studies specifically addressing the impact of OAB medications on nocturia in men were identified [553]. Benefits with combination therapies were not consistently observed.

5.5.3.3 Other medications

Agents to promote sleep [568], diuretics [569], non-steroidal anti-inflammatory agents (NSAIDs) [570] and phytotherapy [571] were reported as being associated with response or QoL improvement [553]. Effect size of these medications in nocturia is generally small, or not significantly different from placebo. Larger responses have been reported for some medications, but larger scale confirmatory RCTs are lacking. Agents to promote sleep do not appear to reduce nocturnal voiding frequency but may help patients return to sleep.

Summary of evidence	LE
No clinical trial of pathophysiology-directed primary therapy has been undertaken.	4
No robust clinical trial of behavioural therapy as primary intervention has been undertaken.	4
Antidiuretic therapy reduces nocturnal voiding frequency in men with baseline severity of two or more voids per night.	1b
There is an increased risk of hyponatremia in patients 65 years of age or older under antidiuretic therapy.	1b
Antidiuretic therapy increases duration of undisturbed sleep.	1b
Alpha 1-blocker use is associated with improvements in undisturbed sleep duration and nocturnal voiding frequency, which are generally of only marginal clinical significance.	2
Antimuscarinic medications can reduce night-time urinary urgency severity, but the reduction in overall nocturia frequency is small or non-significant.	2
Antimuscarinic medications are associated with higher incidence of dry mouth compared with placebo.	2
5α-reductase inhibitors reduce nocturia severity in men with baseline nocturia severity of two or more voids per night.	2
A trial of timed diuretic therapy may be offered to men with nocturia due to nocturnal polyuria. Screening for hyponatremia should be undertaken at baseline and during treatment.	1b

Recommendations	Strength rating
Treat underlying causes of nocturia, including behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	Weak
Discuss behavioural changes with the patient to reduce nocturnal urine volume and episodes of nocturia and improve sleep quality.	Weak
Offer desmopressin to decrease nocturia due to nocturnal polyuria in men < 65 years of age.	Weak
Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria.	Weak
Screen for hyponatremia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatremia.	Strong
Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age.	Strong
Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS.	Weak
Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder.	Weak
Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL).	Weak
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	Weak

5.6 Management of male urinary incontinence

The aim of the following section is to provide evidence-based recommendations for the management of male urinary incontinence.

5.6.1 Epidemiology and Pathophysiology

Urinary incontinence is defined as an unintentional loss of urine and is reported to have a prevalence of 11% in men aged 60 to 64 years old to 31% in men ≥ 85 years and to affect up to 32% of men with LUTS [572-574]. Urinary incontinence can be further classified into three types: stress urinary incontinence (SUI); urgency urinary incontinence (UUI); and mixed urinary incontinence (MUI). Overflow urinary incontinence, post-micturition dribble, nocturnal enuresis, and total incontinence are specific forms of UI that are outside the current scope of this guideline. An overview of the epidemiology and pathophysiology of male UI is given in Table 4.

Table 4: Epidemiology and pathophysiology overview of male UI [574-578].

Type	Definition	Causes and associated factors	Pathophysiology	Clinical presentation
Stress UI: prevalence < 10%	Urine loss during movement or efforts or in general during increased abdominal pressure.	• Benign Prostatic Obstruction surgery • Neurogenic condition • Pelvic surgery • Radical prostatectomy • Urethral surgery	Sphincter deficiency	**Symptoms:** UI during physical activity, exercises, e.g. during coughing, sneezing,no leakage during sleep, no nocturnal enuresis **Voiding diary/Pad test:** with activity **Cough stress test:** leakage can coincide with coughing
Urgency UI: prevalence 40-80%	Urine loss concomitant or immediately following an urgency episode.	• Ageing process • Anorectal dysfunction/GI disorders • Behavioural factors (fluid intake and caffeine consumption) • Chronic BPO • Idiopathic • Intrinsic bladder diseases (cystitis, fibrosis, interstitial cystitis) • Metabolic syndrome • Neurogenic conditions • UTIs	• Detrusor overactivity (neurogenic or not) • Urothelial stimulation • Increased afferent signalling • Others (pelvic organ cross talk, bladder wall ischemia etc.)	**Symptoms:** urgency, usually associated with, increased frequency and nocturia **Voiding diary:** urgency, frequency and nocturia
Mixed UI: prevalence 10-30%	Any combination of SUI and UUI.	Causes of both SIU and UUI	Combination of SUI and UUI	**Symptoms:** UI equally as often with physical activity as with a sense of urgency **Voiding diary:** varies **Cough stress test:** may show leakage with coughing

BPO = benign prostatic obstruction; GI = gastrointestinal; SUI = stress urinary incontinence; UI = urinary incontinence; UTI = urinary tract infection; UUI = urgency urinary incontinence

*5.6.2 **Diagnostic Evaluation***

Medical history and physical examination of males with UI is the same as for male LUTS and should allow UI to be categorised into SUI, UUI or MUI and to identify other types of UI (overflow UI, nocturnal enuresis), or those who need rapid referral to an appropriate specialist (e.g., pelvic diseases, neurological conditions).

Specific validated questionnaires can help to quantify UI severity; however, a detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of this guideline. For more information on available questionnaires see the 6th ICI review on patient reported outcomes assessment [579].

Voiding diaries are a standardised method of measuring symptom severity, including frequency and extent of UI episodes, voided volume and 24-hour or nocturnal total urine volume [43].

Pad tests can be used to quantify severity of UI and to monitor patient's response to treatment although the usefulness of these tests in predicting outcome of treatment is uncertain. Despite this, early post-operative testing with pad tests may predict future continence in men after prostatectomy [580, 581].

Urodynamic testing (multichannel cystometry, video-urodynamics) and specific tests of urethral function (urethral pressure profilometry, Valsalva leak point pressure, retrograde urethral resistance) should be considered on an individual basis, such as in cases when invasive treatment is considered. A Cochrane review showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery, while there is limited evidence that it should be used for the assessment of post prostatectomy UI [579].

Post-void residual volume measurement can be applied with caution to men with non-neurogenic UI, as the prevalence, severity, and clinical application of PVR in men with UI is uncertain.

Imaging (US, MRI, CT scan) can improve the understanding of the anatomical and functional abnormalities that may cause UI and thus help its management [582].

Urinalysis: Reagent strip ('dipstick') urinalysis may indicate UTI, proteinuria, haematuria, or glycosuria, requiring further tests as recommended according to other EAU Guidelines, e.g., Guidelines on urinary tract cancers and urological infections [48-51].

Summary of evidence	**LE**
Validated specific symptom score questionnaires and voiding diaries assist in the screening for and categorisation of UI.	3
Pad test can be used to quantify the presence and severity of UI, as well as a patient's response to treatment.	3
There is limited evidence that urodynamics and PVR affect treatment choice in men with uncomplicated UI .	3

Recommendation	**Strength rating**
Take a complete medical history including symptoms and comorbidities, medications, and a focused physical examination in the evaluation of men with urinary incontinence (UI).	Strong
Use a validated symptom score questionnaire, bladder diary and pad-test to assess UI.	Strong
Measure post-void residual in the assessment of UI.	Strong
Perform urodynamics for UI when considering invasive treatment.	Weak

*5.6.3 **Conservative treatment***

5.6.3.1 Simple clinical interventions

5.6.3.1.1 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI, but most of the evidence for these interventions come from studies with predominately female study populations. However, as many of these interventions are now generalised public health measures their recommendation is in line with general medical practice [583-585].

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated [583, 586]. A cross-sectional population survey found no statistical association between caffeine intake and UI [587]. Conversely, an RCT showed that reduction of caffeine intake, associated with behavioural therapy, resulted in reduced urgency but not UI compared to behavioural therapy alone [588].

5.6.3.1.2 Treatment of comorbidities

Urinary incontinence, especially in the elderly, has been associated with multiple comorbid conditions [589]. It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently suffer from more than one condition. Interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidities or ageing on UI. Although changing drug regimens for underlying diseases may be considered as a possible early intervention, there is limited evidence of benefit [590]. There is also a risk that stopping or altering medication may result in greater harm than benefit.

5.6.3.1.3 Constipation

One RCT, with a majority female population, found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc., reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [591]. However, there is no evidence to show whether treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

5.6.3.1.4 Containment

Containment includes the use of absorbent pads, urinary catheters, external collection devices and penile clamps. A SR of six RCTs comparing different types of pads found that pads filled with super absorbent material were better than standard pads [592]. For men with light UI, a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [593].

A Cochrane review compared different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [594]. A SR of non-randomised studies found no differences in UTI outcome or Upper Urinary Tract (UUT) changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [595]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [596].

An RCT in 56 men with post-prostatectomy incontinence (PPI) compared sheath drainage system, body-worn urinal, penile clamp, and absorbent pads. It was found that the three devices and absorbent pads have different strengths and limitations that make them more (or less) suitable for particular activities. Most men prefer to use a combination of devices and pads to meet their lifestyle needs. Hinge-type penile clamp was good for short vigorous activities as it was the most secure, least likely to leak and most discreet, although almost all men described it as uncomfortable or painful [597].

Summary of evidence	**LE**
There is limited evidence that lifestyle interventions e.g., weight reduction, smoking cessation or diet modification improves UI in males.	3
There is limited evidence that improving comorbidities or changing drug regimens for underlying disease improves UI in males.	3
Pads and/or penile sheaths are palliative options for management of UI.	1b

Recommendation	**Strength rating**
Offer lifestyle advice that may improve urinary incontinence (UI) to patients; however, patients should be informed that the evidence for these interventions is lacking.	Weak
Review any medication associated with the development or worsening of UI.	Weak
Use pads and/or penile sheaths as a palliative option for the management of UI.	Weak

5.6.3.2 Behavioural and Physical therapies

Behavioural and physical therapies encompass all treatments which require a form of self-motivated personal retraining by the patient and include techniques which are used to augment this effect. Usually in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education, and possibly cognitive therapy. Further details for behavioural treatments are outlined in section 5.1.2 of these guidelines.

5.6.3.2.1 Prompted or timed voiding

With prompted voiding, carers rather than the patient, initiate the decision to void. Two SRs confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [598, 599]. Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding, including two RCTs, found inconsistent improvement in continence compared with standard care in cognitively impaired adults [600].

5.6.3.2.2 Bladder training

Bladder training goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes, and restore patient

confidence in controlling bladder function. The ideal form or intensity of a bladder training program for UI is unclear. It is also unclear whether bladder training can prevent the development of UI. The addition of bladder training to anticholinergic therapy did not improve UI compared to antimuscarinics alone, but it did improve frequency and nocturia [601]. In seven RCTs, BT was compared to drug therapy alone and showed only a benefit for oxybutynin in cure and improvement of UI [601].

5.6.3.2.3 Pelvic floor muscle training

A 2015 Cochrane review concluded that there was no overall benefit at twelve months post-surgery for men who received post-operative pelvic floor muscle training (PFMT) for the treatment of PPI and that the benefits of conservative treatment of PPI remain uncertain [602]. However, a subsequent SR and meta-analysis showed that PFMT either alone or in combination with biofeedback and/or electrical stimulation was effective for treating PPI, significantly reducing the time to continence recovery [603]. A further meta-analysis demonstrated that the addition of guided programs using biofeedback and/or pelvic floor muscle electric stimulation (PFES) significantly improved continence recovery rates at one- and three-month intervals post-surgery compared to PFMT alone [604].

Two subsequent SRs in patients who underwent robotic-assisted radical prostatectomy demonstrated that the addition of PFMT to the post-operative management plan shorten the time to continence recovery [605, 606].

Two RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [607, 608]. One RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy, and who had had no previous therapy [609].

One RCT compared PFMT to no treatment in men undergoing TURP. There was no demonstrable difference in the incidence of post-operative incontinence up to twelve months [610]. On the other hand, an RCT in men who underwent HoLEP, demonstrated that PFMT when started pre-operatively promoted early recovery of continence [611].

Other RCTs demonstrated that like PFMT, increased pelvic floor muscle strength and quicker return to continence may be achieved with the Pilates method [612], the oscillating rod [613], a combination of biofeedback with electrostimulation [614] and whole body vibration training [615]. Furthermore, quicker return to continence and improved QoL may be achieved, even with extended and continuing nursing care [616].

5.6.3.2.4 Electrical stimulation

The majority of evidence on electrical stimulation refers to women with SUI and many are of generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters [610].

An RCT of 70 PPI men receiving surface or intra-anal electrostimulation reported a significant reduction in UI in terms of grams of urine loss and a significant improvement in QoL from baseline, but no statistically significant difference between treatment arms [617].

A Cochrane review of six RCTs on electrical stimulation in men with UI concluded that there was some evidence that electrical stimulation enhanced the effect of PFMT in the short-term but not after six months. Electrical stimulation was also more effective than sham stimulation at six, but not twelve months; however, there were more adverse effects including pain and discomfort with electrical stimulation [618].

Electromagnetic stimulation has been promoted as a treatment for UI, but only weak evidence of the short- and long-term effects has been reported in SRs [619, 620].

5.6.3.2.5 Posterior tibial nerve stimulation

Posterior tibial nerve stimulation (PTNS) has been studied as a treatment of UI, especially UUI. Electrical stimulation of the posterior tibial nerve delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done either percutaneously using a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS) or transcutaneously using surface electrodes (T-PTNS). Percutaneous PTNS treatment cycles typically consist of twelve weekly treatments of 30 minutes and T-PTNS treatment cycles typically consists of self-administered, twenty-minute daily sessions, after adequate education.

A female-predominant sham controlled RCT, assessed effectiveness of PTNS in OAB population. There were 22.8% and 20% males in the treatment and sham arms, respectively [621]. Overactive bladder symptoms improved significantly in 54.5% of patients in the PTNS arm compared to 20.9% in the sham arm. A non-inferiority RCT comparing T-PTNS compared to P-PTNS, reported significant improvements in daytime frequency, urgency and UUI episodes without significant difference between treatment arms after twelve weeks of therapy [622]. A SR on T-PTNS in idiopathic and neurogenic female-predominant (males < 10%) population, reported significant improvement in OAB symptoms in 48-93% of patients and cure of UUI episodes in 25-45% [623].

For PTNS, mild pain and discomfort at the puncture site is the most common adverse event [624]. Small haematomas, swelling, leg tingling and vasovagal reaction to needle placement have also been reported [621]. Treatment adherence is generally high at 89.7% [622]. Contra-indications include a cardiac pacemaker and skin disease at the site of stimulation.

There is some evidence that PTNS may benefit male patients with OAB, but due to too insufficient data, no recommendation on PTNS in males can be made at this time. However, considering the safety of this therapy, it can be offered to male patients as an alternative option prior to more invasive treatments.

Summary of evidence	LE
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI but may improve frequency and nocturia.	1b
There is conflicting evidence on whether the addition of bladder training, electrostimulation or biofeedback increases the effectiveness of PFMT alone.	1b
Pre-operative PFMT does not confer additional benefit to men undergoing radical prostatectomy.	1b
Electrical stimulation may add benefit to PFMT up to six months.	2
Electrical stimulation may improve UI compared to sham up to six months.	2
There is limited evidence for the effectiveness of PTNS in male population.	2
There is no evidence that PTNS cures UUI in male population.	2

Recommendations	Strength rating
Implement prompted voiding for patients with urinary incontinence (UI) where appropriate.	Strong
Offer bladder training as a complementary treatment for UI.	Weak
Offer pelvic floor muscle training alone or in combination with biofeedback and/or electrostimulation to men undergoing radical prostatectomy to speed recovery from UI.	Weak

*5.6.4 **Pharmacological management***

5.6.4.1 Drugs for urgency urinary incontinence

Muscarinic receptor antagonists [625-628] and beta-3 agonist [295-297, 629-632] are currently the first-line pharmacological treatments for UUI. The mechanism of action, efficacy, and safety and tolerability profiles of both classes of drugs are discussed in detail in sections 5.2.3 and 5.2.4, respectively.

5.6.4.2 Drugs for stress urinary incontinence

A SR of eight studies evaluating the efficacy of duloxetine in postprostatectomy SUI reported that duloxetine resulted in a mean dry rate of 58% (25–89%), mean improvement in pad number of 61% (12–100%), and mean improvement in one-hour pad weight of 68% (53–90%), at short-term follow-up (mean one to nine months) [633]. However, mean adverse event rates were high, and treatment was discontinued in 38% of cases. The overall certainty of the evidence was low due to study heterogeneity and methodological limitations. Further RCTs with long-term follow-up are required.

Summary of evidence	LE
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	1b
Mirabegron is superior to placebo and as efficacious as antimuscarinics for improvement of UUI.	1b
Duloxetine led to a short-term improvement in postprostatectomy SUI symptoms and QoL improvement; however, a significant proportion of men discontinued treatment.	1b

Recommendations	Strength rating
Offer antimuscarinic drugs or mirabegron to adults with urge urinary incontinence who failed conservative treatment.	Strong
Offer duloxetine to men with stress urinary incontinence.	Weak
Inform patients about the possible adverse events of duloxetine and that its use is off label for this indication in Europe.	Strong

5.6.5 *Surgical treatment for stress urinary incontinence*

5.6.5.1 *Bulking agents in men*

Mechanism of Action: Urethral bulking agents work by adding bulk and improving the coaptation of a damaged sphincter zone. They represent a treatment option in men with either small volume leak or those unfit for more invasive treatment options [634].

Efficacy: A Cochrane review on surgical treatment of PPI identified only one RCT that fulfilled the inclusion criteria. This trial randomised 45 men to Macroplastique injection or artificial urinary sphincter (AUS) implantation and compared their outcomes at 48 months [634]. Significant improvement was reported in both groups for men with minimal incontinence, but in men with total incontinence there was a significant difference in continence rates favouring AUS implantation (72% vs. 23%) [635]. A SR of eight studies (n=142) in men using Macroplastique, Opsys, Durasphere and Urolastic, showed short-term improvement, and reported dry rates between 0-83% [634]. A propensity score-matched analysis of 104 men with PPI, compared submucosal injection of Macroplastique to transobturator male sling (TiLOOP male) [636]. At twelve months follow-up, the reported failure free rates were 15.4% and 76.9%, the daily use of 0-1 pads was 21.2% and 67.3% and the satisfaction rate was 3.8% and 71.2%, respectively. Several small cohort studies of several different bulking agents have not shown any benefit.

A narrative review including data from 25 articles, reports a success rate with all bulking procedures of 54.3%, with 37.5% of symptoms improvement and almost 30% of dryness [637].

In a SR and meta-analysis, three studies addressed bulking agents. Two of them, involving a total of 384 participants, showed a pooled short-term cure rate of 26.1% and a single study on 68 subjects reported a 10.3% long term cure rate. Short- and long-term reoperation rates were not described [638].

Tolerability and safety: Bulking agent associated dysuria and haematuria are frequently reported to be transient and self-resolving [634]. The risk of urinary retention requiring, clean intermittent self-catheterisation (CISC) or long-term catheter use is minimal [639]. However, they may provoke allergic reactions [640] and carry a potential risk for migration [641] to proximal and distal lymph nodes [642]. Overall, post procedural urinary retention rates range between 3-17%, with rare need for temporary catheterization, while post-operatory urinary tract infections ranged from 6-7% [637].

Practical considerations: Bulking agents have shown low cure rates but remain an option for men unfit for more invasive treatment options.

Summary of evidence	**LE**
There is very limited evidence that bulking agents are effective for the treatment of PPI.	2

Recommendation	**Strength rating**
Do not offer bulking agents to men with postprostatectomy incontinence.	Weak

5.6.5.2 *Male Slings*

Male slings have been introduced to treat mild-to-moderate PPI. However, the definitions of mild and moderate UI are unclear. The majority of studies define cure as ‘no pad use’ or ‘one security pad per 24-hours’. Some authors used more strict criteria such as ‘urine loss of less than 2 g per 24-hour pad test’ [643].

5.6.5.2.1 Non-adjustable slings

Mechanism of Action: Non-adjustable male slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery, and it cannot be re-adjusted post-operatively. Synthetic slings restore continence in males either by urethral compression and/or by repositioning the bulb of urethra [644, 645].

Efficacy: A SR and meta-analysis involving 33 prospective cohorts and one RCT comparing sling to AUS, reported that both options are effective in improving UI and QoL [646]. Following sling insertion, the overall cure rate was 60% (95% CI: 0.51-0.67) and 56% (95% CI: 0.44-0.68) for slings and AUS, respectively. The 24-hour pad use was -3.33 (95% CI: -4.33 to -2.34) and -3.75 (95% CI: -4.56 to -2.93) for slings and AUS, respectively. Similar findings were reported by a network meta-analysis that showed comparable efficacy between slings and AUS [647].

The MASTER Trial, a non-inferiority RCT comparing the outcomes of continence surgery in men with bothersome urodynamic SUI, using a very strict definition of UI after prostate surgery, reported that at twelve-

months incontinence rates were 87% for male sling vs. 84.2% for AUS (95% CI: -11.6-4.6, P_{NI}=0.003]), confirming non-inferiority [648]. The subgroup analysis suggested that male sling is inferior to AUS for men with greater incontinence at baseline (pad weight > 250g); however, the difference did not reach statistical significance.

For the re-positioning sling (AdVance™ and AdVanceXP©), a mean subjective cure rate of 49% (8.6 - 73.7%) after mean follow-up of three years has been reported for 136 patients [649]. A prospective multicentre cohort study, with 60-month follow-up, in men with AdVanceXP© demonstrated a constant continence outcome over time with a 57.6% cure rate, 25.4% improvement rate and 16.9% failure rate. These findings were verified in an additional study which reported cure rates of 66.7% and 71.7%, improvement rates of 26.5% and 24.4% and failures rates of 6.9% and 13.3% at 24- and 48-months, respectively [650]. A retrospective comparative study showed that both options are safe and effective in the treatment of male SUI [651].

With the transobturator compressive I-Stop TOMS male sling, 38% of men were dry at twelve months, but this reduced to 23% and 15% after four and five years, respectively [652].

Tolerability and safety: A SR and meta-analysis of 1,170 men with SUI and male sling, reported that the predictors of failure are prior radiation, severity of incontinence and previous surgeries [653]. Pelvic radiotherapy has also been reported in other studies as a negative prognostic factor [654]. A comparison among radiated vs. non-radiated men who had AdVanceXP reported a greater degree of post-operative improvement in the non-radiated group (49.6% vs. 22.2%) as well as greater satisfaction rates (95% vs. 64%) [655]. The most common complication with male slings is pain and local superficial wound infection [656]. Chronic pain has been observed in 1.3% of men who had non-adjustable slings [656]. Post-operative transient voiding dysfunction occurred in 4.3-10.3%, mostly as *de novo* urgency or urinary retention, while erosions and chronic pain were uncommon (0-0.4%), as was explantation [649, 650, 657-659].

Practical considerations: Fixed male slings are considered safe and improve continence, but their efficacy is limited in men with severe incontinence or previous radiotherapy.

5.6.5.2.2 Adjustable slings in males

Mechanism of Action: Adjustable slings in males are those for which the tension of the sling can be adjusted post-operatively. Three main systems have been used in men: the Remeex® system [660], the Argus® system [661] and the ATOMS® system [662].

Efficacy: There is one small RCT for adjustable slings in males [663]. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success [660, 662-666]. A SR reported objective cure rates varying between 17-92% after adjustable sling implantation [656].

For the Remeex® system, only two studies, with conflicting findings, have been published. One study followed nineteen patients for nearly seven years and reported 70% success, with no explants, infections, or erosions [660]. The second study followed fourteen patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [664].

Data on the Argus® system has been reported for 404 men, but only few series have reported on more than 40 patients, with the longest follow-up being 35-months. Success rates varied between 17-93%, with a mean of 73.0% reporting subjective cure [665, 666]. A head-to-head comparison between the two Argus systems reported similar efficacy outcomes at 44 months, but Argus T was associated with a higher inguinal pain and explantation rate [667]. A small study of 22 men with PPI randomised to AdVance or Argus T reported superior 24-hour pad test results and of patient satisfaction levels for Argus T at eighteen-months follow-up [663].

A SR of the ATOMS system reported the pooled evidence from 1,393 patients with a 67% dryness, 90% improvement after adjustment and 16.4% complication rate [662]. The expulsion rate was 5.75%. Another SR and meta-analysis with 3,059 patients reported that ATOMS was superior to ProACT in mean dryness rate (68% vs. 55%), overall improvement (91% vs. 80%), satisfaction rate (87% vs. 56%), mean number of filing adjustments (2.4 vs. 3.5) and post-operative pad use per day (1.1 vs. 2.1) [668].

Tolerability and Safety: The most frequent complications in adjustable male slings are pain, erosions, and infections [656]. Pain at the implant site was usually only temporary, but chronic pain has been reported in 1.5% of men [665, 666]. The number of implants requiring re-adjustment is reported between 8-38.6% [666, 669, 670]. Explantation rates range from 10-15.8% and erosion rate is estimated around 10% [653]. The most

common reasons for explantation are device infection (4.1-8%), erosions (4-12%), and urethral perforations (2.7-16%). A SR reported a device explantation rate of 5% vs. 25% and a major complication rate of 4.2% vs. 10.4% for ATOMS and ProACT, respectively [668].

Practical considerations: There is no evidence that adjustability offers additional benefit as RCTs are lacking; therefore, no recommendation can be made at this time. Explantation rate seems superior to fixed male sling based on external comparisons.

5.6.5.2.3 Autologous slings

The strategy of intra-operative placement of an autologous vas deferens sling below the vesico-urethral anastomosis during robotic-assisted radical prostatectomy (RARP) has been explored with the intention to improve early return of continence. Two RCTs [671, 672] showed an advantage of sling vs. no sling at one-month follow-up, and another study [673] showed an advantage of a 6-branch vs. a 2-branch sling at one month follow-up. However, a larger RCT (n=195), showed that continence rate and near-continence rate were similar between groups at six months with 66% vs. 65% and 86% vs. 88%, respectively [674].

Summary of evidence	**LE**
There is limited short-, medium- and long-term evidence that fixed transobturator male slings cure or improve PPI in patients with mild-to-moderate incontinence.	1b
Men with severe incontinence, previous radiotherapy or transurethral surgery may have less benefit from fixed transobturator male slings.	2
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is no evidence that adjustability offers additional benefit over other types of slings.	3
There is no evidence that intra-operative placement of an autologous sling during RARP improves return of continence at six months.	1b

Recommendations	**Strength rating**
Offer non-adjustable transobturator slings to men with mild-to-moderate* post-prostatectomy incontinence.	Weak
Inform men that severe incontinence, prior pelvic radiotherapy or transurethral surgery may worsen the outcome of non-adjustable male sling surgery.	Weak

** The terms "mild" and "moderate" PPI remain undefined.*

5.6.5.3 Compression devices in males

5.6.5.3.1 Artificial urinary sphincter

Mechanism of action: The AUS is the standard treatment for moderate-to-severe male SUI. The AMS 800 three component system with inflatable cuff, control pump and pressure regulating balloon is the device with the longest follow-up and the greatest level of evidence [675]. The ZSI 375 is a two-component device, inflatable cuff, and control pump, allowing an easier implantation process [676]. Other AUS devices have been launched e.g., the Victo and Br-SL-AS 904 systems, but robust evidence regarding their efficacy and safety is pending [677].

Efficacy A meta-analysis of 33 cohort studies and one RCT, reported significant improvement after AUS implantation in overall cure rates (56%) and reductions in pad used per 24-hours (-3.75) [646]. Several observational studies reported on functional outcomes after AMS 800. Social continence rates (0-1 pads used daily) ranged from 55-76.8% [678-680]. A 77.2% continence rate and 89.5% subjective satisfaction rate have been reported after median follow-up of > 15 years in 57 men who had undergone AUS placement [681]. A prospective cohort study of 40 patients with a mean follow-up of 53 months, showed that from all urodynamic parameters only low bladder compliance had a negative impact on outcome [682]. However, another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [683]. Some recent multicenter studies have confirmed older statements that surgeon's experience and higher surgical volume is associated with better outcomes and a lower revision rate after AUS implantation [684, 685].

The data regarding ZSI 375 is limited. A retrospective, non-randomised trial across several centres in Europe, reported an 84.4% success rate (19.3% dry rate and 65.1% improved 0-1 pads per day) after 43 months [676]. A 72% success rate was reported at seven years follow-up for 45 patients who underwent placement of the ZSI 375 device in France [686].

Tolerability and safety: Artificial urinary sphincter complications include device infection/erosion (8.5%), mechanical failure (6.2%) and urethral atrophy (7.9%) [687]. In multivariate analysis, radiation therapy was

independently associated with risk of urethral atrophy, as were older age and a longer time interval between prostate cancer treatment and AUS surgery [680]. Urethral erosion is associated with previous irradiation and penoscrotal approach [688]. The reported revision rates at three years for any reason were 10-29.1% [678, 688-690]. The risk of urethral erosion after ZSI 375 AUS is 8.2-13.3% and risk of mechanical failure is 2.2-2.5% [676].

Practical Considerations: Artificial urinary sphincter is efficacious and improves the QoL of men with PPI. To minimise complications, it is advised to refer patients to specialised centres experienced in AUS implementation. Men considering insertion of an AUS should be fully informed that the success of the intervention relies on their ability to operate the pump. Treating physicians should keep in mind that operating the AUS may become difficult in men who develop cognitive impairment or lose manual dexterity. Artificial urinary sphincter has a limited lifespan and 'maintenance' re-operations are common in the long-term. These re-interventions should not be classified as complications [675].

5.6.5.3.2 Non-circumferential compression device (ProACT®)

Mechanism of action: The ProACT® system consists of two devices. Each device includes the balloon, the bi-lumen tubing, and the volume-adjustment port. The devices are introduced by a trocar via two small perineal incisions and are placed under fluoroscopic guidance on each side of the bladder neck, close to the vesico-urethral anastomotic site. The balloons can be filled, and their volume can be adjusted post-operatively using a hypodermic needle injected through the intra-scrotal port.

Efficacy: A SR and meta-analysis of nineteen studies including 1,264 patients reported a 60.2% dry rate, significant reduction in number of pads used per day (-3.1) and greatly improved QoL scores for ProACT® [691]: however, the level of heterogeneity among the included studies was high. A comparison between ATOMS and ProACT®, showed that the former is associated with higher improvement and satisfaction rates and fewer complications [668]. A quasi-randomised trial comparing ProACT® with bone-anchored male slings found that both resulted in similar improvements in SUI (68% vs. 65%, respectively) [692]. A questionnaire study showed that 50% of patients were still significantly bothered by persistent incontinence following ProACT® [693]. A subgroup analysis of radiotherapy patients reported worst outcomes as compared to patients not receiving radiotherapy (46% vs. 68% success rate) as well as a higher percentage of urethral erosion for ProACT® [694].

Tolerability and safety: The most common intra-operative complication during ProACT® implantation is perforation of the bladder and/or urethra. A meta-analysis estimated a perforation rate of 5.3% [691]. The estimated overall revision rate is 22.2%, and the main causes are erosion (3.8%), device leaking (4.1%) and migration (6.5%) [691]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [692, 693, 695-697].

Practical Considerations: ProACT® has a satisfactory rate of success and seems to be a reasonable alternative for the treatment of male UI; however, it is associated with high complication rates.

Summary of evidence	**LE**
Primary AUS implantation is effective for cure of SUI in men.	1b
There are conflicting data on whether previous pelvic radiotherapy affects the outcome of AUS implantation.	3
The non-circumferential compression device (ProACT®) is effective for treatment of PPI SUI; however, it is associated with a high failure and complication rate leading to frequent explantation particularly after pelvic radiation therapy.	2b
The rate of explantation of the AUS due to infection or erosion remains high (up to 24% in some series).	3

Recommendations	**Strength rating**
Offer artificial urinary sphincter (AUS) to men with moderate-to-severe stress urinary incontinence.	Strong
Implantation of AUS or ProACT® for men should only be offered in expert centres.	Weak
Warn men receiving AUS or ProACT® that, although cure can be achieved there is a high risk of complications, mechanical failure, and the need for explantation.	Strong
Do not offer non-circumferential compression device (ProACT®) to men who have had pelvic radiotherapy.	Weak

5.6.6 ***Surgical treatment for urgency urinary incontinence***

5.6.6.1 *Bladder wall injection of botulinum Toxin A*

Mechanism of action: The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [541]. Onabotulinum toxin A (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory non-neurogenic UUI in adults [698, 699].

Efficacy: An RCT of OAB-wet patients whose symptoms were not adequately managed with anticholinergics and who receive either bladder wall injections of onabotA (100 U) or saline reported a 50% reduction in UUI episodes/day whilst the number of micturitions/day reduced by more than two in patients receiving onabotA [700]. A total of 22.9% of the patients in the onabotA arm were fully dry vs. 6.5% in the saline arm.

A SR and meta-analysis comparing the efficacy of onabotA, mirabegron and anticholinergics in adults with idiopathic OAB reported that patients who received onabotA (100U) achieved greater reduction in UI episodes, surgery, micturition frequency and the highest odds of achieving dryness as well as > 50% reduction from baseline UI episodes per day [701].

A randomised, placebo-controlled pilot study, assessing the effect of onabotA for the treatment of refractory OAB symptoms after prostatectomy reported significantly improved QoL and ICIQ scores and improvements in daily frequency in patients receiving onabotA compared to placebo [702]. A retrospective trial assessed onabotA efficacy in 65 non-obstructed men with refractory OAB and reported significant improvement in UDI-6 score (-4.2) and IIQ-7 (-6.0) scores, compared to baseline [703].

In a retrospective, single-centre cohort study onabotA treatment for OAB in 120 patients lead to lower CISC rates in male patients after prior de-obstructive surgery than in surgery-naïve patients (28.6% CISC in the group without prior surgery, 7.5% in the TURP subgroup, and 4.2% in the radical prostatectomy subgroup) [704].

A phase IIIb trial randomised solifenacin-naive patients (10% males) with refractory OAB to onabotA, solifenacin or placebo, and showed that patients receiving onabotA had significantly greater changes in UI episodes (-3.19) compared to solifenacin (-2.6) and placebo (-1.33) [705].

A network meta-analysis (male population range 9.8-40.2%) which compared onabotA to mirabegron demonstrated that onabotA was associated with improved outcomes in frequency episodes per day (-0.43 [-1.22-0.37]) and in UI episodes per day (-0.46 [-1.46-0.53]) [706].

Tolerability and safety: Urinary retention and UTIs are the two most common adverse events after onabotA injection. Other reported adverse events include haematuria, dysuria and post-treatment pain [707]. Compared to mirabegron, onabotA is associated with higher risk for UTI and treatment emergent adverse events [706]. A retrospective analysis compared the use of CISC after onabotA injection, among men who had previous prostatectomy vs. those without prior surgery [704]. A 7.5% catheterisation rate after TURP, 4.2% rate after radical prostatectomy and 28.6% rate in men without prior prostate surgery was reported.

Practical Considerations: BoNT-A injections is a recommended treatment option for men with refractory UUI. Despite the lack of a universally accepted injection protocol, gender specific studies and absence of studies in BPO patients, BoNT-A seems superior to medical therapy. It is associated with a higher UTIs and urinary retention risk, coupled with the need for repeated injections. A dedicated series in male population, focused on treatment persistence, has shown a high discontinuation rate [708]. Patients treated for OAB with onabotA treatment that have not undergone prior de-obstruction are more likely to develop retention and subsequent CISC.

Summary of evidence	**LE**
A single treatment session of onabotA (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and QoL.	1b
There is no evidence that repeated injections of onabotA have reduced efficacy, but discontinuation rates are high.	3
There is an increased risk of retention and UTI with onabotA injections.	2

Recommendations	Strength rating
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy.	Weak
Warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need for clean intermittent self-catheterisation (ensure that they are willing and able to do so).	Strong

5.6.6.2 Sacral nerve stimulation (neuromodulation)

Mechanism of action: Sacral nerve stimulation (SNS) delivers low amplitude electrical impulses to the sacral nerve roots via an electrode implanted adjacent to the third sacral nerve root and connected to an attached pulse generator implanted in the buttock. It works by modulating neural activity thus stabilising bladder electrical activity through an unknown mechanism. It is a two-stage process: in the first stage, a tined lead electrode is placed percutaneously near the S3 root and linked to an external stimulator to assess the response. If symptoms reduced more than 50%, patients are candidates for the second stage which is the full implant.

Efficacy: Several trials assess the clinical effectiveness of SNS. All RCTs suffer from the limitation that patients and assessors cannot be blinded to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. In addition, the percentage of male population in these trials is around 10%. A meta-analysis compared the effectiveness of SNS to onabotA and reported no significant difference in successfully treated cases at six-month follow-up (RR 0.93; 95% CI: 0.63-1.39) [709].

Tolerability and safety: Main complications after SNS are pain at the implant site (13-42%), lead migration (4.0-21%), leg or back pain (3.0-18%) and wound infection (5.7-6.7%). Surgical revision is required in 29-33% of patients due to device malfunction, battery or device replacement or lead migration [710].

Practical Considerations: SNS represents an alternative to onabotA in patients with refractory OAB, as it has shown good success rates and an acceptable safety profile.

Summary of evidence	LE
Sacral nerve stimulation is effective after failed conservative treatment for OAB/UUI, but no sham controls have been used.	2a

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have urgency urinary incontinence refractory to medical therapy and are willing to undergo surgical treatment.	Weak

5.6.6.3 Cystoplasty/urinary diversion

Mechanism of action: Augmentation cystoplasty involves the interposition of a detubularised segment of bowel into the bivalved bladder wall, aiming to increase bladder capacity and reduce OAB related symptoms. Urinary diversion remains a reconstructive option for patients with intractable UI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation.

Efficacy: There are no RCTs comparing bladder augmentation to other treatments for patients with refractory OAB/UUI. In a large study with three years follow-up augmentation cystoplasty resulted in a post-operative continence rate of 93% in idiopathic detrusor overactivity patients, 78% in neurogenic overactivity and up to 90% when an artificial urinary sphincter was implanted, respectively [711]. The largest case series of bladder augmentation in an idiopathic population included only women [712]. At an average follow up of 75.4 months only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. A small prospective mixed gender trial reported high patient satisfaction rates with augmentation cystoplasty vs. onabotA therapy [713]. A small study comparing ileal with colonic conduits concluded that there were no differences in the relative risks of UUT infection and uretero-intestinal stenosis [714]. However, there are no studies that have specifically examined these techniques in the treatment of intractable OAB/UUI [714]. Therefore, careful consideration on which operation is undertaken will depend on thorough pre-operative counselling, access to stoma/continence nurses as well as patient factors to allow for fully informed patient choice.

Tolerability and safety: Cystoplasty and urinary diversion are major urologic operations. The early post-operative complications include infection, bowel obstruction, bleeding, and cardiorespiratory complications.

Long-term complications include metabolic disturbances (hyperchloraemic metabolic acidosis), change in bowel habits, increased mucus production, stone formation, bladder perforation and rarely bladder cancer [715]. Following augmentation cystoplasty or diversion, the majority of patients will depend on self-catheterisation for bladder emptying. Patients with urinary conduit will depend on lifelong urine bags.

Practical Considerations: Augmentation cystoplasty and urinary diversion represent realistic treatment options for men with refractory OAB. However, both options involve a major operation, with a non-negligible long-term complication rate and a lifelong reliance on catheterisation or urine bags.

Summary of evidence	**LE**
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic OAB.	3
The need to perform CISC following augmentation cystoplasty is high.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term complications.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3

Recommendations	**Strength rating**
Offer augmentation cystoplasty to patients with overactive bladder (OAB)/urgency urinary incontinence (UUI) who have failed all other treatment options and are able and willing to perform self-catheterisation.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of complications; the risk of having to perform clean intermittent self-catheterisation and the need for life-long surveillance.	Strong
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of OAB/UUI, who will accept a stoma.	Weak

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS, uroflowmetry, and PVR volume.

6.2 Medical treatment

Patients receiving α1-blockers, muscarinic receptor antagonists, beta-3 agonists, PDE5Is or the combination of α1-blockers and 5-ARIs or muscarinic receptor antagonists should be reviewed four to six weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS, uroflowmetry, and PVR volume. Frequency volume charts or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after twelve weeks and six months to determine their response and adverse events. The following are recommended at follow-up visits: history, IPSS, uroflowmetry and PVR volume. Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is greater than ten years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at six months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day three and seven, one month after initiating therapy and periodically during treatment. If serum sodium concentration has remained normal during periodic screening follow-up screening can be carried out every three months subsequently. However, serum sodium concentration should be monitored more frequently in patients $\geq$ 65 years of age and in patients at increased risk of hyponatremia. The following tests are recommended at follow-up visits: serum-sodium concentration and FVC. The follow-up sequence should be restarted after dose escalation.

6.3 Surgical treatment

After prostate surgery, patients should be reviewed four to six weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary. The following tests are recommended at follow-up visit after four to six weeks: IPSS, uroflowmetry and PVR volume.

Summary of evidence	LE
Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations, but not on evidence-based studies.	4

Recommendations	Strength rating
Follow-up all patients who receive conservative, medical, or surgical management.	Weak
Define follow-up intervals and examinations according to the specific treatment.	Weak

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8. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic Male LUTS Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative and travel and meeting expenses. No honoraria or other reimbursements have been provided.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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1. INTRODUCTION

1.1 Aim

The European Association of Urology (EAU) Paediatric Urology Guidelines Panel has prepared these Guidelines with the aim of increasing the quality of care for children with urological conditions. This Guideline document is limited to a number of common clinical pathologies in paediatric urological practice, as covering the entire field of paediatric urology in a single guideline document is unattainable.

The majority of urological clinical problems in children are specialised and in many ways differ to those in adults. This publication intends to outline a practical and preliminary approach to paediatric urological conditions. Complex and rare conditions that require special care with experienced doctors should be referred to designated centres where paediatric urology practice has been fully established and a multidisciplinary team is available.

Over time, paediatric urology has developed and matured, establishing its diverse body of knowledge and expertise and may now be ready to distinguish itself from its parent specialties. Thus, paediatric urology has recently emerged in many European countries as a distinct subspecialty of both urology and paediatric surgery and presents a unique challenge in the sense that it covers a large area with many different schools of thought and a huge diversity in management.

Knowledge gained by increasing experience, new technological advances and non-invasive diagnostic screening modalities has had a profound influence on treatment modalities in paediatric urology, a trend that is likely to continue in the years to come.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of children and their caregivers into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Paediatric Urology Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website: http://uroweb.org/guideline/paediatric-urology/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications are also available [1-7]. All documents can be viewed through the EAU website: http://uroweb.org/guideline/paediatric-urology/.

1.4 Publication history

The Paediatric Urology Guidelines were first published in 2001 [8]. This 2021 publication includes a number of updated chapters and sections as detailed below.

1.5 Summary of changes

The literature for the complete document has been assessed and updated, wherever relevant. Key changes in the 2022 publication:

- Section 3.11 - Monosymptomatic nocturnal enuresis – bedwetting: Both the literature and the text have been extensively updated;
- Section 3.12 - Management of neurogenic bladder: Both the literature and the text have been updated;
- Section 3.16 -Obstructive pathology of renal duplication: ureterocele and ectopic ureter: The literature has been updated resulting in minor amendments to the text;
- Section 3.19 – Rare Conditions – A new section has been added to the section on bladder tumours on eosinophilic cystitis and nephrogenic adenoma.

3.19 Recommendations for rare conditions in children

3.19.2 Papillary tumours of the bladder in children and adolescents - Eosinophilic cystitis and Nephrogenic adenoma

3.19.2.9 Recommendations for papillary tumours of the bladder in children

Recommendations	LE	Strength rating
Have a high index of suspicion of eosinophilic cystitis (EC) in protracted urinary tract symptoms unresponsive to regular treatment.	4	Strong
Remove any possible allergens as the obvious first step in managing EC.	4	Strong
Eosinophilic cystitis can be managed medically with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A.	4	Weak
Manage nephrogenic adenoma (NE) by resection either transuretherally or by open excision.	4	Strong
Regular endoscopic follow-up especially for augmented patients with NA is justified.	4	Weak

2. METHODS

2.1 Introduction

These Guidelines were compiled based on current literature following a structured review. Databases covered by the searches included Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. Application of a structured analysis of the literature was not possible in many conditions due to a lack of well-designed studies. The limited availability of large randomised controlled trials (RCTs) - influenced also by the fact that a considerable number of treatment options relate to surgical interventions on a large spectrum of different congenital problems - means this document is largely a consensus document. Clearly there is a need for continuous re-evaluation of the information presented in this document.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [9, 10]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [11];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [12]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer review

All chapters of the Paediatric Urology Guidelines were peer-reviewed in 2015.

3. THE GUIDELINE

3.1 Phimosis

This chapter does not deal with neonatal circumcision as practised in the USA, nor mass circumcision as practised in many African countries as part of a national program to prevent HIV. Also "religious and cultural" circumcision is not discussed. At present in some European countries professional organisations do not support circumcision for these reasons and it is no longer covered by insurance in these countries. Special centres have been set up, where well-trained doctors perform circumcisions under sedation and local anaesthetics at a lower cost. In all circumstances facilities have to comply with national regulations regarding hygiene, special equipment, pain protocols and follow-up. Usually these clinics have an agreement with a nearby hospital for the immediate treatment of possible complications. It is estimated that 37-39% of men worldwide are circumcised [13].

3.1.1 Epidemiology, aetiology and pathophysiology

At the end of the first year of life, retraction of the foreskin behind the glandular sulcus is possible in approximately 50% of boys; this increases to approximately 89% by the age of three years. The incidence of phimosis is 8% in six to seven year olds and in just 1% in males aged sixteen to eighteen years [14].

3.1.2 Classification systems

Phimosis is either primary with no sign of scarring, or secondary (pathological) to a scarring such as balanitis xerotica obliterans (BXO) [14]. Balanitis xerotica obliterans, also termed lichen sclerosis, has been recently found in 35% of circumcised prepuce in children and adolescents and in 17% of boys younger than ten years presenting with phimosis. The clinical appearance of BXO in children may be confusing and does not always correlate with the final histopathological results. Lymphocyte-mediated chronic inflammatory disease was the most common finding [15, 16] (LE: 2b).

Phimosis has to be distinguished from normal agglutination (adhesion) of the foreskin to the glans, which is a more or less lasting physiological phenomenon with clearly-visible meatus and partial retraction [17]. Separation of the prepuce from the glans is based on accumulated epithelial debris (smegma) and penile erections. Forceful preputial retraction should be discouraged to avoid cicatrix formation [18].

Paraphimosis must be regarded as an emergency situation: retraction of a too narrow prepuce behind the glans penis into the glanular sulcus may constrict the shaft and lead to oedema of the glans and retracted foreskin. It interferes with perfusion distally from the constrictive ring and brings a risk of preputial necrosis.

3.1.3 Diagnostic evaluation

The diagnosis of phimosis and paraphimosis is made by physical examination. If the prepuce is not retractable, or only partly retractable, and shows a constrictive ring on drawing back over the glans penis, a disproportion between the width of the foreskin and the diameter of the glans penis has to be assumed. In addition to the constricted foreskin, there may be adhesions between the inner surface of the prepuce and the glanular epithelium and/or a fraenulum breve. Paraphimosis is characterised by a retracted foreskin with the constrictive ring localised at the level of the sulcus, which prevents replacement of the foreskin over the glans.

3.1.4 Management

Conservative treatment is an option for primary phimosis. The class 4 therapies were more effective over placebo and manual stretching [19]. A corticoid ointment or cream (0.05-0.1%) can be administered twice a day over a period of 4-8 weeks with a success rate of > 80% [20-23] (LE: 1b). A recurrence rate of up to 17% can be expected [24]. This treatment has no side effects and the mean bloodcortisol levels are not significantly different from an untreated group of patients [25] (LE: 1b). The hypothalamic pituitary-adrenal axis was not influenced by local corticoid treatment [26]. Adhesion of the foreskin to the glans does not respond to steroid treatment [20] (LE: 2).

Operative treatment of phimosis in children is dependent on the caregivers' preferences and can be plastic or radical circumcision after completion of the second year of life. Alternatively, the Shang Ring may be used especially in developing countries [27]. Plastic circumcision has the objective of achieving a wide foreskin circumference with full retractability, while the foreskin is preserved (dorsal incision, partial circumcision, trident preputial plasty, combining 2 Z-plasties and a Y plasty) [28, 29]. However, this procedure carries the potential for recurrence of the phimosis [30]. In the same session, adhesions are released and an associated fraenulum breve is corrected by fraenulotomy. Meatoplasty is added if necessary. In all cases meticulous haemostasis is mandatory and absorbable interrupted sutures are most often used.

An absolute indication for circumcision is secondary phimosis. In primary phimosis (including those not responding to medical treatment), recurrent balanoposthitis and recurrent urinary tract infections

(UTIs) in patients with urinary tract abnormalities are indications for surgical intervention [31-34] (LE: 2b). Male circumcision significantly reduces the bacterial colonisation of the glans penis with regard to both non-uropathogenic and uropathogenic bacteria [35](LE: 2b). Simple ballooning of the foreskin during micturition is not a strict indication for circumcision.

Routine neonatal circumcision to prevent penile carcinoma is not indicated. A meta-analysis could not find any risk in uncircumcised patients without a history of phimosis [36]. Contraindications for circumcision are: an acute local infection and congenital anomalies of the penis, particularly hypospadias or buried penis, as the foreskin may be required for a reconstructive procedure [37, 38]. Circumcision can be performed in children with coagulopathy with 1-5% suffering complications (bleeding), if haemostatic agents or a diathermic blade are used [39, 40]. Childhood circumcision has an appreciable morbidity and should not be recommended without a medical reason and also taking into account epidemiological and social aspects [41-45] (LE: 1b). Balanitis xerotica obliterans is associated with meatal pathology (stenosis) after circumcision in up to 20% of boys and adjuvant local steroid treatment is advised [16, 46].

Treatment of paraphimosis consists of manual compression of the oedematous tissue with a subsequent attempt to retract the tightened foreskin over the glans penis. Injection of hyaluronidase beneath the narrow band or 20% mannitol may be helpful to release the foreskin [47, 48] (LE: 3-4). If this manoeuvre fails, a dorsal incision of the constrictive ring is required. Depending on the local findings, a circumcision is carried out immediately or can be performed in a second session.

*3.1.5 **Complications***

Complications following circumcision vary and have been reported between 0-30% [45]. In a recent study Hung *et al*. found during a 5-year follow-up period 2.9% complications in non-neonates of which 2.2% were early (within 30 days after circumcision). Non-healing wounds, haemorrhage, wound infection, meatal stenosis, redundant skin and non-satisfying cosmetic appearance as well as cicatrix formation and trapped penis all may occur [49].

*3.1.6 **Follow-up***

Any surgery done on the prepuce requires an early follow-up of four to six weeks after surgery.

*3.1.7 **Summary of evidence and recommendations for the management of phimosis***

Summary of evidence	LE
Treatment for phimosis usually starts after two years of age or according to caregivers' preference.	3
In primary phimosis, conservative treatment with a third generation corticoid ointment or cream is a first-line treatment with a success rate of more than 80%.	1b

Recommendations	LE	Strength rating
Offer corticoid ointment or cream to treat primary symptomatic phimosis.	1b	Strong
Circumcision will also solve the problem.	2b	Strong
Treat primary phimosis in patients with recurrent urinary tract infection and/or with urinary tract abnormalities.	2b	Strong
Circumcise in case of lichen sclerosus or scarred phimosis.	2b	Strong
Treat paraphimosis by manual reposition and proceed to surgery if it fails.	3	Strong
Avoid retraction of asymptomatic preputial adhesions.	2b	Weak

3.2 Management of undescended testes

*3.2.1 **Background***

Cryptorchidism or undescended testis is one of the most common congenital malformations of male neonates. Incidence varies and depends on gestational age, affecting 1.0-4.6% of full-term and 1.1-45% of preterm neonates. Following spontaneous descent within the first months of life, nearly 1.0% of all full-term male infants still have undescended testes at one year of age [50]. This congenital malformation may affect both sides in up to 30% of cases [51]. In newborn cases with non-palpable or undescended testes on both sides and any sign of disorders of sex development (DSDs) like concomitant hypospadias, urgent endocrinological and genetic evaluation is required [52].

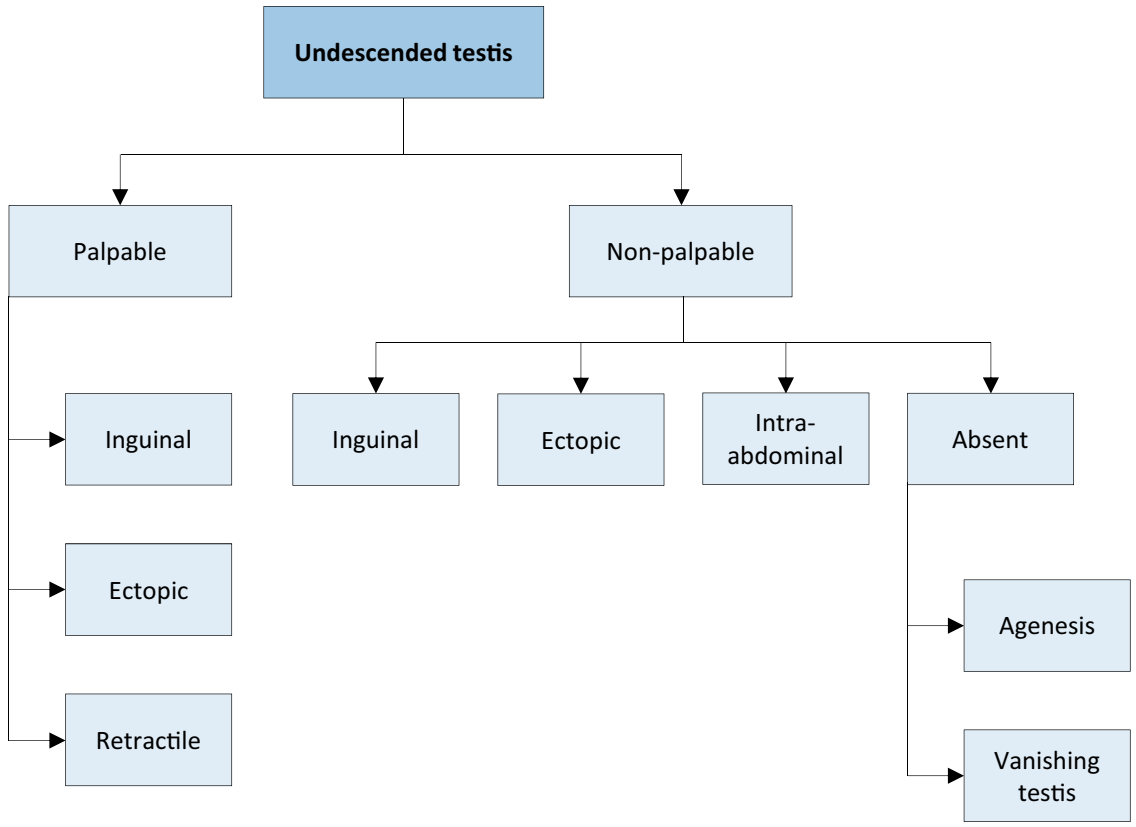
*3.2.2 **Classification***

The term cryptorchidism is most often used synonymously for undescended testes. The most useful classification of undescended testes is distinguishing into palpable and non-palpable testes, and clinical

management is decided by the location and presence of the testes (see Figure 1). Approximately 80% of all undescended testes are palpable [53]. Acquired undescended testes can be caused by entrapment after herniorrhaphy or spontaneously referred to as ascending testis.

Palpable testes include true undescended testes and ectopic testes. Non-palpable testes include intra-abdominal, inguinal, absent, and sometimes also some ectopic testes. Most importantly, the diagnosis of palpable or non-palpable testis needs to be confirmed once the child is under general anaesthesia, as this is the first step of any surgical procedure for undescended testes.

Figure 1: Classification of undescended testes



3.2.2.1 Palpable testes

Undescended testes

A true undescended testis is on its normal path of descent but is halted on its way down to the scrotum. Depending on the location, the testes may be palpable or not, as in the case of testes arrested in the inguinal canal.

Ectopic testes

If the position of a testis is outside its normal path of descent and outside the scrotum, the testis is considered to be ectopic. The most common aberrant position is in the superficial inguinal pouch. Sometimes an ectopic testis can be identified in a femoral, perineal, pubic, penile or even contralateral position. Usually, there is no possibility for an ectopic testis to descend spontaneously to the correct position; therefore, it requires surgical intervention. In addition, an ectopic testis might not be palpable due to its position.

Retractile testes

Retractile testes have completed their descent into a proper scrotal position but can be found again in a suprascrotal position along the path of their normal descent. This is due to an overactive cremasteric reflex [54]. Retractile testes can be easily manipulated down to the scrotum and remain there at least temporarily.

They are typically normal in size and consistency. However, they may not be normal and should be monitored carefully since up to one-third can ascend and become undescended [55].

3.2.2.2 Non-palpable testes

Among the 20% of non-palpable testes, 50-60% are intra-abdominal, canalicular or peeping (right inside the internal inguinal ring). The remaining 20% are absent and 30% are atrophic or rudimentary.

Intra-abdominal testes

Intra-abdominal testes can be located in different positions, with most of them being found close to the internal inguinal ring. However, possible locations include the kidney, anterior abdominal wall, and retrovesical space. In the case of an open internal inguinal ring, the testis may be peeping into the inguinal canal.

Absent testes

Monorchidism can be identified in up to 4% of boys with undescended testes, and anorchidism (bilateral absence) in < 1%. Possible pathogenic mechanisms include testicular agenesis and atrophy after intrauterine torsion with the latter one most probably due to an *in utero* infarction of a normal testis by gonadal vessel torsion. The term "vanishing testis" is commonly used for this condition [56].

3.2.3 ***Diagnostic evaluation***

History taking and physical examination are key in evaluating boys with undescended testes. Localisation studies using different imaging modalities are usually without any additional benefit.

3.2.3.1 History

Caregivers should be asked for maternal and paternal risk factors, including hormonal exposure and genetic or hormonal disorders. If the child has a history of previously descended testes this might be suggestive of testicular ascent [57]. Prior inguinal surgery is indicative of secondary undescended testes due to entrapment.

3.2.3.2 Physical examination

An undescended testis is pursued by carefully advancing the examining fingers along the inguinal canal towards the pubis region, perhaps with the help of lubricant. A possible inguinal testis can be felt to bounce under the fingers [58]. A non-palpable testis in the supine position may become palpable once the child is in a sitting or squatting position. If no testis can be identified along the normal path of descent, possible ectopic locations must be considered.

In the event of unilateral non-palpable testis, the contralateral testis needs to be examined. Its size and location can have important prognostic implications. Any compensatory hypertrophy suggests testicular absence or atrophy [59]. Nevertheless, this does not preclude surgical exploration since the sign of compensatory hypertrophy is not specific enough [60, 61].

In the event of bilateral undescended testes and any evidence or sign of DSDs, such as genital ambiguity, or scrotal hyperpigmentation, further evaluation including endocrinological and genetic assessment becomes mandatory [62].

3.2.3.3 Imaging studies

Imaging studies cannot determine with certainty that a testis is present or not [63]. Ultrasound (US) lacks the diagnostic sensitivity to detect the testis confidently or establish the absence of an intra-abdominal testis [64]. Consequently, the use of different imaging modalities, such as US or Magnetic resonance imaging (MRI) [65], for undescended testes is limited and only recommended in specific and selected clinical scenarios (e.g. identification of Müllerian structures in cases with suspicion of DSDs) [64].

3.2.4 ***Management***

Treatment should be started at the age of six months. After that age, undescended testes rarely descend [66]. Any kind of treatment leading to a scrotally positioned testis should be finished by twelve months, or eighteen months at the latest, because histological examination of undescended testes at that age has already revealed a progressive loss of germ cells and Leydig cells [67]. The early timing of treatment is also driven by the final adult results on spermatogenesis and hormone production, as well as on the risk of tumour development [68].

3.2.4.1 Medical therapy

Unfortunately, most of the studies on hormonal treatment have been of poor quality, with heterogeneous and mixed patient populations, testis location, schedules and dosages of hormonal administration. Additionally, long-term data are almost completely lacking.

Short-term side effects of hormonal treatment include increased scrotal erythema and pigmentation, and induction of pubic hair and penile growth. Some boys experience pain after intramuscular injection of human chorionic gonadotropin (hCG). All of these tend to regress after treatment cessation [69, 70].

3.2.4.1.1 Medical therapy for testicular descent

Hormonal therapy using hCG or gonadotropin-releasing hormone (GnRH) is based on the hormonal dependence of testicular descent, but has a limited success rate of only 20% [71]. However, it must be taken into account that almost 20% of these descended testes have the risk of re-ascending later [72]. In general, success rates depend on testicular location. The higher the testis is located prior to therapy, the lower the success rate, suggesting that testicular position is an important determinant of success [69]. Some authors recommend combined hCG-GnRH treatment. Unfortunately, it is poorly documented and the treatment groups were diverse. Some studies reported successful descent in up to 38% of non-responders to monotherapy [73]. The Panel consensus is that endocrine treatment to achieve testicular descent is not recommended (LE: 4).

Human chorionic gonadotropin

Human chorionic gonadotropin (hCG) stimulates endogenous testosterone production and is administered by intramuscular injection. Several dose and administration schedules are reported. There is no proven difference between 1.5 IU and weight-based doses up to 3.0 IU every other day for fourteen days [74]. Similar response rates were achieved with 500 IU once weekly and 1.50 IU three times weekly [75]. However, there is evidence that dosing frequency might affect testicular descent rates. Fewer lower dose injections per week for five weeks seem to be superior to one higher dose every seven to ten days for three weeks with regard to testicular descent [76].

Gonadotropin-releasing hormone

Gonadotropin-releasing hormone (GnRH) analogues (e.g., buserelin and gonadorelin) are available as nasal sprays, thus avoiding painful intramuscular injections. A typical dosage regimen consists of 1.2 mg per day in three divided doses, for four weeks. Success rates are wide ranging, from 9 to 60%, due to multiple treatment strategies and heterogeneous patient populations [77].

3.2.4.1.2 Medical therapy for fertility potential

Hormonal treatment may improve fertility indices [77, 78] and therefore serve as an additional tool to orchidopexy. There is no difference in treatment with GnRH before (neo-adjuvant) or after (adjuvant) surgical orchidolysis and orchidopexy in terms of increasing fertility index, which may be a predictor for fertility later in life [79]. It is still unknown whether this effect on testicular histology persists into adulthood but it has been shown that men who were treated in childhood with buserelin had better semen analyses compared with men who had childhood orchidopexy alone or placebo treatment [77].

It is reported that hCG treatment may be harmful to future spermatogenesis through increased apoptosis of germ cells, including acute inflammatory changes in the testes and reduced testicular volume in adulthood [80].

Identification of specific subgroups of boys with undescended testes who would benefit from such an approach using hormones is difficult. Since these important data on specific groups as well as additional support on the long-term effects are still lacking, the Nordic consensus does not recommend hormonal therapy [81]. The consensus of the Panel is to recommend endocrine treatment with GnRH analogues in a dosage described above for boys with bilateral undescended testes to preserve the fertility potential (LE: 4).

3.2.4.2 Surgical therapy

If a testis has not concluded its descent at the age of six months (corrected for gestational age), and since spontaneous testicular descent is unlikely to occur after that age, surgery should be performed within the subsequent year, and by age eighteen months at the latest [68]. In addition, early orchidopexy can be followed by partial catch-up testicular growth, which is not the case in delayed surgery [79]. All these findings recommend performing early orchidopexy between the ages of six and twelve months [66]. But despite early and successful orchiopexy within the first year of life up to 25% of boys with non-syndromic undescended testes may be at risk for infertility based on hormonal and histological data, as a recently published series on 333 boys showed. This is especially true for bilateral cases, but in addition in about 5% of unilateral cases reduced numbers of germ cells were detected in testicular biopsies as well [82].

3.2.4.2.1 Palpable testes

Surgery for palpable testes includes orchidofunicolysis and orchidopexy, either via an inguinal or scrotal approach. The latter approach is mainly reserved for low-positioned, undescended testes, with the pros and cons of each method being weighed against each other [83].

3.2.4.2.1.1 Inguinal orchidopexy

Inguinal orchidopexy is a widely used technique with a high success rate of up to 92% [84]. Important steps include mobilisation of the testis and spermatic cord to the level of the internal inguinal ring, with dissection and division of all cremasteric fibres, to prevent secondary retraction and detachment of the gubernaculum

testis. The patent processus vaginalis needs to be ligated proximally at the level of the internal ring, because an unidentified or inadequately repaired patent processus vaginalis is an important factor leading to failure of orchidopexy [85]. Any additional pathology has to be taken care of, such as removal of an appendix testis (hydatid of Morgagni). At this moment the size of the testis can be measured and the connection of the epididimis to the testis can be judged and described in the protocol. Some boys have a significant dissociation between testis and epididymis which is prognostically bad for fertility. Finally, the mobilised testicle needs to be placed in a sub-dartos pouch within the hemi-scrotum without any tension. If the length achieved using the above-mentioned technique is still inadequate, the Prentiss manoeuvre, which consists of dividing the inferior epigastric vessels and transposing the spermatic cord medially, in order to provide a straight course to the scrotum, might be an option [86]. With regard to fixation sutures, if required, they should be made between the tunica vaginalis and the dartos musculature [87]. Lymph drainage of a testis that has undergone surgery for orchidopexy may have changed from high retroperitoneal drainage to iliac and inguinal drainage, which might become important in the event of later malignancy [88].

3.2.4.2.1.2 Scrotal orchidopexy

Low-positioned, palpable undescended testis can be fixed through a scrotal incision including division of the gubernaculum, and the processus vaginalis needs to be probed to check for patency [89]. Otherwise, fixation in the scrotum is carried out correspondingly to the inguinal approach. In up to 20% of cases, an inguinal incision will be compulsory to correct an associated inguinal hernia [90]. Any testicular or epididymal appendages can be easily identified and removed. A systematic review shows that the overall success rates ranged from 88 to 100%, with rates of recurrence and post-operative testicular atrophy or hypotrophy < 1% [83]. Another recently published systematic review and meta-analysis revealed similar outcome data regarding post-operative complications, including wound infection, testicular atrophy, testicular reascent, and hernia for palpable low positioned undescended testes. The only significant difference was the shorter operative time [91].

3.2.4.2.2 Non-palpable testes

For non-palpable testes, surgery must clearly determine whether a testis is present or not [92]. If a testis is found, the decision has to be made to remove it or bring it down to the scrotum. An important step in surgery is a thorough re-examination once the boy is under general anaesthesia, since a previously non-palpable testis might be identifiable and subsequently change the surgical approach to standard inguinal orchidopexy, as described above. Otherwise, the easiest and most accurate way to locate an intra-abdominal testis is diagnostic laparoscopy [93]. Subsequent removal or orchidolysis and orchidopexy can be carried out using the same approach to achieve the therapeutic aims [94]. Some tend to start with inguinal surgical exploration, with possible laparoscopy during the procedure [95]. If an ipsilateral scrotal nubbin is suspected, and contralateral compensatory testicular hypertrophy is present, a scrotal incision with removal of the nubbin, thus confirming the vanishing testis, is an option avoiding the need for laparoscopy [96].

During laparoscopy for non-palpable testes, possible anatomical findings include spermatic vessels entering the inguinal canal (40%), an intra-abdominal (40%) or peeping (10%) testis, or blind-ending spermatic vessels confirming vanishing testis (10%) [97].

If there is a vanishing testis, the procedure is finished once blind-ending spermatic vessels are clearly identified. If the vessels enter the inguinal canal, an atrophic testis may be found upon inguinal exploration or a healthy testis that needs to undergo standard orchidopexy [98]. A peeping testis can be placed down in the scrotum laparoscopically or via an inguinal incision [99]. Placement of an intra-abdominal testis can sometimes be a surgical challenge. Usually, testes lying > 2 cm above the internal inguinal ring may not reach the scrotum without division of the testicular vessels [100]. Under such circumstances, a Fowler-Stephens orchidopexy may be an option [101] (see Figure 2).

Proximal cutting and transection of the testicular vessels, with conservation of the collateral arterial blood supply, via the deferential artery and cremasteric vessels comprise the key features of the Fowler-Stephens procedure. Recently, a modification with low spermatic vessel ligation has gained popularity, allowing blood supply from the testicular artery to the deferential artery. An additional advantage is the position of the peritoneal incision, leading to a longer structure, to ease later scrotal placement [102]. Due to the nature of these approaches the testis is at risk of hypotrophy or atrophy if the collateral blood supply is insufficient [103]. The testicular survival rate in the one-stage Fowler-Stephens technique varies between 50 and 65% based on post-operative Doppler-ultrasound findings [104]. For two-stage procedures success rates increase up to 90% [105]. The advantages of two-stage orchidopexy, with the second part done usually six months after the first, are to allow for development of collateral blood supply and to create greater testicular mobility [106]. In addition, preservation of the gubernaculum may also decrease the chance of testicular atrophy [107]. An alternative might be microsurgical auto-transplantation, which has a success rate of up to 90%. However, this approach requires skilled and experienced surgeons and is performed in a limited number of centres [108].

3.2.4.2.3 Complications of surgical therapy

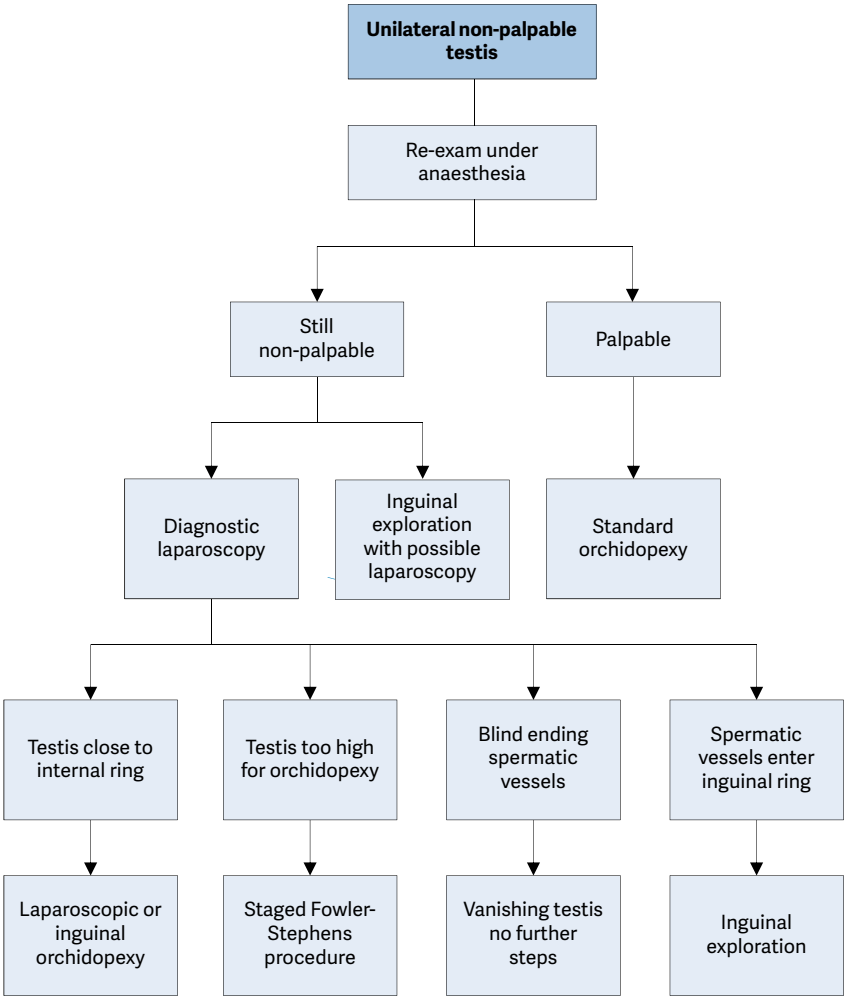
Surgical complications are usually uncommon, with testicular atrophy being the most serious. A systematic review revealed an overall atrophy rate for primary orchidopexy of 1.83%, 28.1% for one-stage Fowler-Stephens procedure, and 8.2% for the two-stage approach [109]. Other rare complications comprise testicular ascent and vas deferens injury besides local wound infection, dehiscence, and haematoma.

3.2.4.2.4 Surgical therapy for undescended testes after puberty

A study on 51 men diagnosed with inguinal unilateral undescended testis and a normal contralateral one, with no history of any previous therapy, demonstrated a wide range of changes upon histological evaluation. Nearly half of the study population still had significant germ cell activity at different maturation levels. Importantly, the incidence of intratubular germ cell neoplasia was 2% [110].

The Panel consensus recommends orchiectomy in post-pubertal boys with an undescended testis and a normal contralateral one in a scrotal position.

Figure 2: Treatment of unilateral non-palpable undescended testes



*3.2.5 **Undescended testes and fertility***

The association of undescended testes with compromised fertility [111] is extensively discussed in the literature and seems to be a result of multiple factors, including germ cell loss, impaired germ cell maturation [112], Leydig cell diminution and testicular fibrosis [113].

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as those with bilateral descended testes. Boys with bilateral undescended testes suffer both lower fertility and paternity rates. Fertility rate is the number of offspring born per mating pair, individual or population whereas paternity reflects the actual potential of fatherhood [114]. The age at which surgical intervention for an undescended testis occurs seems to be an important predictive factor for fertility later in life. Endocrinological studies revealed higher inhibin-B and lower follicle-stimulating hormone (FSH) levels in men who underwent orchidopexy at two years of age compared to individuals who had surgery later, which is indicative of a benefit of earlier orchidopexy [115]. In addition, others demonstrated a relation between undescended testes

and increased loss of germ cells and Leydig cells, which is also suggestive of prompt orchidopexy being a significant factor for fertility preservation [116]. Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [113].

In summary, early surgical correction of undescended testes is highly recommended before twelve months of age, and by eighteen months at the latest for preservation of fertility potential [67].

*3.2.6 **Undescended testes and malignancy***

Boys who are treated for an undescended testis have an increased risk of developing testicular malignancy. Screening and self-examination both during and after puberty is therefore recommended [117]. A Swedish study, with a cohort of almost 17,000 men (56 developed a testicular tumour) who were treated surgically for undescended testes and followed for 210,000 person-years, showed that management of undescended testes before the onset of puberty decreased the risk of testicular cancer. The relative risk of testicular cancer among those who underwent orchidopexy before thirteen years of age was 2.2 compared to the Swedish general population; this increased to 5.4 for those treated after thirteen years of age [118].

A systematic review and meta-analysis of the literature have also concluded that pre-pubertal orchidopexy may reduce the risk of testicular cancer and that early surgical intervention is indicated in boys with undescended testes [119].

*3.2.7 **Summary of evidence and recommendations for the management of undescended testes***

Summary of evidence	**LE**
An undescended testis justifies treatment early in life to avoid loss of spermatogenic potential.	2a
A failed or delayed orchidopexy may increase the risk of testicular malignancy later in life.	2a
The earlier the treatment, the lower the risk of impaired fertility and testicular cancer.	2a
In unilateral undescended testis, fertility rate is reduced whereas paternity rate is not.	1b
In bilateral undescended testes, fertility and paternity rates are impaired.	1b
The treatment of choice for undescended testis is surgical replacement in the scrotum.	1b
The palpable testis is usually treated surgically using an inguinal approach.	2b
The non-palpable testis is most commonly approached laparoscopically.	2b
There is no consensus on the use of hormonal treatment.	2b

Recommendations	**LE**	**Strength rating**
Do not offer medical or surgical treatment for retractile testes instead undertake close follow-up on a yearly basis until puberty.	2a	Strong
Perform surgical orchidolysis and orchidopexy before the age of twelve months, and by eighteen months at the latest.	2b	Strong
Evaluate male neonates with bilateral non-palpable testes for possible disorders of sex development.	1b	Strong
Perform a diagnostic laparoscopy to locate an intra-abdominal testicle.	1a	Strong
Hormonal therapy in unilateral undescended testes is of no benefit for future paternity.	2a	Strong
Offer endocrine treatment in case of bilateral undescended testes.	4	Weak
Inform the patient/caregivers about the increased risk of a later malignancy with an undescended testis in a post-pubertal boy or older and discuss removal in case of a contralateral normal testis in a scrotal position.	3	Weak

3.3 Testicular Tumours in prepubertal boys

*3.3.1 **Introduction***

Testicular tumours account for approximately 1-2% of all paediatric solid tumours [120]. Testicular tumours in prepubertal boys differ in several aspects to testicular tumours in adolescent and adult men: they have a lower incidence, they have a different histologic distribution (teratomas and yolk sac tumours are more common and germ cell tumours are less common) and they are more often benign. A recent epidemiological study showed that in children under the age of 15 years the incidence is highest in Asia (4.2 per million) and South America (5 per million) and lowest in Europe (2.1 per million) and North America (2.5 per million). This is in contrast to the incidence in adolescent and young adults where the highest incidence is in Europe (137.4 per million), and North America (94.9 per million), while a lower incidence was observed in South and Central America (66.5 per million) and Asia (27.1 per million) [121]. For age distribution in prepubertal boys, there is a small peak around

the age of two years [122]. Some recent studies demonstrated that up to 60-75% of the tumours are benign [120, 123-127]. Intratubular neoplasia (TIN) is practically non-existent in children [128-131]. Testicular tumours can generally be classified as germ cell or stromal tumours. One specific tumour type is the gonadoblastoma, which contains germ cell and stromal cell tumour types and will occur almost exclusively in the setting of disorders of sexual differentiation [132].

In the past 30 years, it has clearly been shown, that there is a fundamental difference between testicular tumours in childhood and those in adulthood - not only in terms of the difference and incidence [121] but also in terms of histology [128]. In prepubertal boys, most intratesticular tumours are benign, whereas post puberty the tumours are most likely malignant.

*3.3.2 **Clinical presentation***

Clinical presentation is a painless scrotal mass in more than 90% of the patients, detected by the caregiver, physician or the patient himself. A history of a trauma, pain or hernia is rare. A hydrocele can be found in 15 – 50% [124, 133]. In boys with early onset of puberty (e.g. early penile and prepubic hair growth) as well as high testosterone and low gonadotropin levels, a Leydig cell tumour should be excluded [134].

In patients presenting with a scrotal mass, paratesticular tumours should also be taken into account as a differential diagnosis. However, these are even less common compared to intratesticular tumours. The spectrum of paratesticular tumours includes benign tumours such as leiomyoma, fibroma, lipoma, haemangioma, cystic lymphangioma and lipoblastoma as well as malignant tumours such as the paratesticular rhabdomyosarcoma with an excellent prognosis and the rare melanotic neuroectodermal tumour of infancy with a high recurrence rate [135-138]. As most of them are benign, intra-operative frozen section should be available during surgery. An organ sparing surgical approach is preferred in benign tumours, whereas in malignant tumour standard orchiectomy is carried out.

*3.3.3 **Evaluation***

To confirm the diagnosis, a high-resolution ultrasound (US) examination (7.5 – 12.5 MHz), preferably a doppler ultrasound, is required. The detection rate is almost 100% [139-142]. With high-resolution US, microlithiasis - small hyperdense areas without sound shadows - is increasingly seen in prepubertal boys. A recent meta-analysis showed that only 4 out of 296 boys (< 19 years of age diagnosed with microlithiasis) developed a testicular tumour of whom two previously had a testicular tumour on the opposite or ipsilateral site [143]. If microlithiasis shows up in patients with additional risk factors for testicular tumour, then the caregivers/patients should be informed about the increased risk and encouraged to carry out regular self-examinations - similar to patients treated for undescended testis [144]. There is no evidence, that regular sonographic follow-up is useful [143]. The risk for infertility may be higher in patients with microlithiasis and if these patients have any sign of infertility later, the risk of developing a tumour seems to be higher compared to patients without microlithiasis and infertility [145]. Due to the low incidence of a contralateral tumour, even in cases of testicular microlithiasis, there is no indication for contralateral testicular biopsy in prepubertal boys.

Age should be taken into account, when tumour markers are used. Human chorionic gonadotropin (ß-hCG) is derived from chorion carcinoma, embryonal carcinoma or seminoma. However, these tumours are extremely rare in prepubertal boys and therefore ß-hCG is not useful in prepubertal boys. Alpha-fetoprotein (AFP) has a clear limitation of its sensitivity and specificity in the first months of life [133] and sometimes takes up to twelve months before the serum concentration reaches the known standard values (< 10 ng/mL) [127, 146]. It is produced by > 90% of yolk sac tumours. Teratomas can also produce AFP, but not to that extent of yolk sac tumours [147]. Alpha-fetoprotein should be measured before any therapeutic intervention (tumour enucleation/ orchiectomy) and ideally should be available at the time of the procedure. Alpha-fetoprotein has a serum biological half-life of five days and should be measured five days after tumour resection/orchiectomy in those with an elevated AFP. There is no urgent need for pre-operative staging, as this has no consequence before the definitive histology is available.

*3.3.4 **Treatment/Management***

If a testicular tumour is suspected, surgery with the option of intra-operative frozen section should be performed. It is not necessary to do this as an emergency procedure. However, in order to confirm the diagnosis and to avoid familial anxiety, the operation should be scheduled as soon as possible, preferably within the next few days. Organ-preserving surgery should be performed, whenever possible. A recent published review article showed that out of 227 patients with organ-sparing surgery only two cases (one in a patient with an epidermoid cyst and one in a patient with a mature teratoma) had a recurrence [148-150].

Orchiectomy could be considered only if normal testicular parenchyma is no longer detectable in the pre-operatively high-resolution ultrasound and/or the AFP is > 100 ng/mL in a > 12-month-old boy: highly suspicious of a yolk sac tumour.

For surgical technique, the Panel is in favour of an inguinal approach. Furthermore, clamping of the vessels has the advantage of a better view, when organ sparing surgery is performed. However, there is no evidence in the literature, that tumour-spread is prevented by clamping the vessels. Whenever possible, testis sparing surgery should be performed along with frozen sections during surgery to confirm the diagnosis (begin vs. malignant tumour) and to confirm if a microscopically margin-negative resection is performed, in which no gross or microscopic tumour remains in the primary tumour bed (R0 resection). In cases of an R0 resection, the tunica is closed and the testis is replaced in the scrotum. In case of R1 resection (removal of all macroscopic disease, but microscopic margins are positive for tumour) confirmed by frozen section in a malignant or potential malignant tumour, an orchiectomy should be performed at the same time of surgery. If the final pathology later demonstrates a R1 resection in a malignant tumour despite intra-operative negative margins on frozen section, an inguinal orchiectomy can safely be performed.

In patients with a malignant tumour (yolk sac tumour, immature teratoma) staging should be performed including an MRI of the abdomen and a CT-scan from the chest. If there is any suspicion of a non-organ confined tumour, the patient should be referred to a paediatric oncologist. In patients with the rare diagnosis of a Granulosa cell tumour, imaging of the abdomen to exclude enlarged lymph nodes is reasonable as this may be a potentially malignant tumour; in those with Sertoli or a Leydig cell tumour, an MRI is recommended, as 10% are malignant and the metastases do not respond very well to chemotherapy or radiation in the adult literature [151, 152]. The TNM classification from 2015 for adult testicular tumours can be used in patients with a malignant tumour [153]. In benign tumours (mature teratoma, epidermoid cysts) no further staging is required.

*3.3.5 **Tumour entities in prepubertal boys***

Teratomas are usually benign in prepubertal children and represent the greatest proportion of intratesticular tumours (around 40%) [120, 154]. They present at a median age of 13 months (0-18 months). Only in adolescent and adults, they should be considered as malignant tumours. Histologically they can consist of a combination of the three primitive embryological germ-cell layers (ectoderm, mesoderm and endoderm). Most of these elements shows microscopically mature elements [155]; however, some immature teratomas in this age group have also been reported [156]. To exclude any malignant potential, like focal areas of a yolk-sac tumour, the entire specimen should be investigated. On US examination a heterogenous picture with some calcification is seen [157] and AFP should be less than 100 ng/mL in an infant. After organ-sparing surgery only one recurrence was reported in the literature [150].

Epidermoid cysts are of ectodermal origin and seem to be related to well-differentiated teratomas; they are always benign [155]. Keratin-producing epithelium is responsible for the keratinised-squamous-epithelial deposits, which appear hyperechogenic in an US [157]. Organ-sparing surgery should be performed and if confirmed by histology, there is no need for surveillance despite the fact that one “recurrence” has been reported thirteen years after diagnosis [149].

Juvenile granulosa cell tumours occur usually in the first year of life, typically within the first six months [158]. They are well circumscribed and have a typical yellow-tan appearance; 2/3 have cystic elements, 1/3 solid [158]. The stroma can be fibrous or fibromyxoid. So far, no recurrence has been reported after organ-sparing surgery [158, 159].

Leydig cell tumours arising from the testosterone producing Leydig cells should be suspected in boys with early onset of puberty with high testosterone and low gonadotropin levels [134]. Patients are usually between six and ten years of age; the tumours are well circumscribed with yellow-brown nodules. In children there are no reports of malignant Leydig cell tumours and after organ sparing surgery, there are no reported recurrences to date [160, 161]. In the adult literature, there is a malignancy rate of 10% reported and primary retroperitoneal lymphadenectomy should be discussed in cases with enlarged lymph nodes, as these metastases do not respond very well to chemotherapy or radiation [162].

Around 1/5 of the Sertoli-cell tumours occur in children; usually within the first year of life [163]. In the paediatric age group, the large-cell calcifying Sertoli cell tumours (LCCSCT) are the most common tumour variant [164, 165]. They can occur in patients with complex dysplastic syndromes, such as the Carney or Peutz-Jeghers syndrome [165-167]. Except one case report with the histological diagnosis of a malignant LCCSCT [164], all other reported tumours are benign, therefore organ-sparing surgery should be performed.

Yolk sac tumours are the predominant prepubertal malignant germ cell tumours and may represent around 15% of the prepubertal tumours in boys [120]. They also have a number of other names: endodermal sinus tumours, juvenile embryonal carcinoma, clear cell carcinoma, orchioblastoma, vitellineum, archenteronoma and sometimes extraembryonal mesoblastoma [168]. They are histologically mostly solid, yellow-grey tumours. They occur usually within the first two years of life [169]. Up to 80-85% of the tumours are organ confined (Stage I) [170]. The tumour usually spreads haematogenously (chest). Twenty percent of those with Stage I disease may develop visible metastasis in 20% within the next two years. In a German study, 14 out of 91 patients with Stage I had a recurrence after observation – all were cured by chemotherapy alone. Four out of five with metastatic disease initially, were cured by chemotherapy after radical orchiectomy [171]. In a recent published series from China, 21 out of 90 paediatric patients with a Stage I yolk sac tumour received primary chemotherapy. One of the 21 had a recurrence, whereas 29 out of 69 who underwent surveillance after initial orchiectomy had a recurrence. The overall four-year survival rate was 97.8% [169], almost the same recurrence rate has also been reported by American oncology groups [172, 173]. Therefore in patients with Stage I disease (no metastatic disease in the MRI-abdomen and CT scan of the chest as well as normal age-adapted AFP values) close follow-up together with the paediatric oncologists including AFP every two to three months and MRI of the abdomen is recommended, at least for the first two to three years [133]. This is especially recommended in those with invasions of the lymphatic vessels, as this has been shown to be a prognostic factor in one of the recent series [169]. In cases of recurrence, chemotherapy should be performed by paediatric oncologists according to national study protocols.

*3.3.6 **Follow-up***

Regular US examination is recommended in the follow-up period to detect any recurrence and/or other abnormalities. As there are only a few studies with recurrence after testicular sparing surgery or orchiectomy, no clear recommendation can be made concerning the interval and the duration of follow-up. However, doing an US examination every three to six months within the first year seems reasonable, as few recurrences have been detected at this time and the rate of atrophy is extremely low after organ-sparing surgery [148]. Only in patients with a malignant tumour, regular follow-up examination after the first year of surgery seems reasonable (see above). The follow-up in patients with a Leydig cell tumour should include endocrinological examinations. Using the SEER data base, the five-year relative survival for testicular malignancies for patients < 14 years of age diagnosed with localised testicular cancer was 97.4%, and for those with distant disease 72.6% [174].

*3.3.7 **Congenital Adrenal Hyperplasia***

Boys with a congenital adrenal hyperplasia (CAH) represent a special group. Up to a third of the patients have so-called testicular adrenal rest tumours (TARTs) This proportion increase with age [175, 176]. It is most likely to be ectopic adrenal cells, which are growing under pathological stimulation from Adrenocorticotropic Hormone (ACTH) [177]. They have no malignant potential, but they can have a lasting impact on fertility by displacing the normal testicular parenchyma [177, 178]. These patients should be offered US screening and advice on fertility with the option of cryopreservation [178]. As far as is known, no malignant tumour has been described in patients with a typical TART. As a result, the indication for surgical intervention in these patients to rule out a malignant tumour should be offered very cautiously.

Summary of evidence	**LE**
Testicular tumours in prepubertal boys have a lower incidence and a different histologic distribution compared to the adolescent and adult patients.	2a
In prepupertal boys up to 60-75% of testicular tumours are benign.	3

Recommendations	**LE**	**Strength rating**
High-resolution ultrasound (7.5 – 12.5 MHz), preferably a doppler ultrasound, should be performed to confirm the diagnosis.	3	Strong
Alpha-fetoprotein (AFP) should be determined in prepubertal boys with a testicular tumour before surgery.	2b	Strong
Surgical exploration should be done with the option for frozen section, but not as an emergency operation.	3	Strong
Organ-preserving surgery should be performed in all benign tumours.	3	Strong
Staging (MRI abdomen /CT chest) should only be performed in patients with a malignant tumour to exclude metastases.	3	Strong

Magnetic resonance imaging should only be performed in patients with the potential malignant Leydig or Sertoli-cell-tumours to rule out lymph node enlargement.	4	Weak
Patients with a non-organ confined tumour should be referred to paediatric oncologists post-operatively.	4	Weak

3.4 Hydrocele

*3.4.1 **Epidemiology, aetiology and pathophysiology***

Hydrocele is defined as a collection of fluid between the parietal and visceral layers of the tunica vaginalis [179]. Pathogenesis of primary hydrocele is based on patency of the processus vaginalis in contrast with secondary hydrocele. Incomplete obliteration of the processus vaginalis peritonei results in formation of various types of communicating hydrocele; a large open processus vaginalis allowing passage of abdominal viscera results in clinical hernia [180]. The exact time of spontaneous closure of the processus vaginalis is not known. It persists in approximately 80-94% of newborns and in 20% of adults [181]. If complete obliteration of the processus vaginalis occurs with patency of mid-portion, a hydrocele of the cord occurs. Scrotal hydroceles without associated patency of the processus vaginalis are also encountered in newborns [182]. Non-communicating hydroceles, based on an imbalance between the secretion and re-absorption of this fluid, are found secondary to minor trauma, testicular torsion, epididymitis, varicocele operation (due to ligation of the lymphatics) or may appear as a recurrence after primary repair of a communicating or non-communicating hydrocele.

*3.4.2 **Diagnostic evaluation***

The classic description of a communicating hydrocele is that of a hydrocele that fluctuates in size, and is usually related to ambulation. It may be diagnosed by history-taking and physical investigation. Transillumination of the scrotum provides the diagnosis in the majority of cases, keeping in mind that fluid filled intestine and some pre-pubertal tumours may transilluminate as well [183, 184]. If the diagnosis is that of a hydrocele, there will be no history of reducibility and no associated symptoms; the swelling is translucent, smooth and usually not tender. If there are any doubts about the character of an intrascrotal mass, scrotal US should be performed and has nearly 100% sensitivity in detecting intrascrotal lesions. Doppler US studies help to distinguish hydroceles from varicocele and testicular torsion, although these conditions may also be accompanied by a hydrocele.

*3.4.3 **Management***

In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months because of the tendency for spontaneous resolution [185] (LE: 2). Little risk is taken by initial observation as progression to hernia is rare and does not result in incarceration [185]. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology [186, 187] (LE: 2). Persistence of a simple scrotal hydrocele beyond twelve months of age may be an indication for surgical correction. There is no evidence that this type of hydrocele risks testicular damage. The natural history of hydrocele is poorly documented beyond the age of two years and according to a systematic review there is no good evidence to support current practice. Delaying surgery may reduce the number of procedures necessary without increasing morbidity [188].

The question of contralateral disease should be addressed by both history-taking and physical examination at the time of initial consultation [189] (LE: 2). In late-onset hydrocele, suggestive of a non-communicating hydrocele, there is a reasonable chance of spontaneous resolution (75%) and expectant management of six to nine months is recommended [190]. In the paediatric age group, the operation consists of ligation of the patent processus vaginalis or scrotal via inguinal incision and the distal stump is left open, whereas in hydrocele of the cord the cystic mass is excised or unroofed [184, 186, 191, 192] (LE: 4). In expert hands, the incidence of testicular damage during hydrocele or inguinal hernia repair is very low (0.3%) (LE: 3). Laparoscopic hernia repair with percutaneous ligation of the patent processes vaginalis is a minimally invasive alternative to open inguinal herniorrhaphy [193, 194]. Sclerosing agents should not be used because of the risk of chemical peritonitis in communicating processus vaginalis peritonei [184, 186] (LE: 4). The scrotal approach (Lord or Jaboulay technique) is used in the treatment of a secondary non-communicating hydrocele.

*3.4.4 **Summary of evidence and recommendations for the management of hydrocele***

Summary of evidence	**LE**
In the majority of infants, surgical treatment of hydrocele is not indicated within the first twelve months due to the tendency for spontaneous resolution. Little risk is taken by initial observation as progression to hernia is rare.	2a
In the paediatric age group, an operation would generally involve ligation of the patent processus vaginalis via inguinal incision.	4

Recommendations	LE	Strength rating
In the majority of infants, observe hydrocele for twelve months prior to considering surgical treatment.	2a	Strong
Perform early surgery if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.	2b	Strong
Perform a scrotal ultrasound in case of doubt about the character of an intrascrotal mass.	4	Strong
Do not use sclerosing agents because of the risk for chemical peritonitis.	4	Strong

3.5 Acute scrotum

*3.5.1 **Epidemiology, aetiology and pathophysiology***

Acute scrotum is a paediatric urological emergency, most commonly caused by torsion of the testis or appendix testis, or epididymitis/epididymo-orchitis [195-200]. Other causes of acute scrotal pain are idiopathic scrotal oedema, mumps orchitis, varicocele, scrotal haematoma, incarcerated hernia, appendicitis or systemic disease (e.g. Henoch-Schönlein purpura) [201-213]. Trauma can also be a cause of acute scrotum due to post-traumatic haematomas, testicular contusion, rupture, dislocation or torsion [214-219]. Scrotal fat necrosis has also been reported to be an uncommon cause of mild-to-moderate scrotal pain in pre-pubertal overweight boys after exposure to cold [220].

In this chapter testicular torsion and epididymitis are discussed, while recurrent epididymitis is discussed in the chapter dealing with infections. Torsion of the testis occurs most often in the neonatal period and around puberty, whereas torsion of the appendix testis occurs over a wider age range [221]. Epididymitis affects two age groups: less than one year and twelve to fifteen years [222, 223]. One study predicted the annual incidence of epididymitis around 1.2 per 1,000 children [224].

Perinatal torsion of the testis most often occurs prenatally. Bilateral torsion comprises 11-21% of all perinatal cases [225]. Most cases of perinatal torsion are extravaginal, in contrast to the usual intravaginal torsion which occurs during puberty.

*3.5.2 **Diagnostic evaluation***

Patients usually present with scrotal pain, except in neonatal torsion. The sudden onset of invalidating pain in combination with vomiting is typical for torsion of the testis or appendix testis [226, 227].

In general, the duration of symptoms at presentation is shorter in testicular torsion (69% present within twelve hours) and torsion of the appendix testis (62%) compared to epididymitis (31%) [197, 198, 223]. Prepubertal males are more likely to present with atypical symptoms and delayed presentation and diagnosis, leading to delayed surgical intervention and a higher rate of orchiectomy, compared to postpubertal boys [228].

In the early phase, location of the pain can lead to diagnosis. Patients with acute epididymitis experience a tender epididymis, whereas patients with testicular torsion are more likely to have a tender testicle, in case of torsion of the appendix testis there may be isolated tenderness of the superior pole of the testis [223]. An abnormal (horizontal) position of the testis is more frequent in testicular torsion than epididymitis [197]. Looking for absence of the cremasteric reflex is a simple method with 100% sensitivity and 66% specificity for testicular torsion [222, 227] (LE: 3). Elevation of the scrotum may reduce complaints in epididymitis, but not in testicular torsion.

Fever occurs more often in epididymitis (11-19%). The classical sign of a “blue dot” was found only in 10-23% of patients with torsion of the appendix testis [196, 197, 222, 229]. In many cases, it is not easy to determine the cause of acute scrotum based on history and physical examination alone [195-200, 222, 229]. A positive urine culture is only found in a few patients with epididymitis [199, 222, 229, 230]. It should be remembered that a normal urinalysis does not exclude epididymitis. Similarly, an abnormal urinalysis does not exclude testicular torsion.

Doppler US is useful to evaluate acute scrotum, with 63.6-100% sensitivity and 97-100% specificity, a positive predictive value of 100% and negative predictive value of 97.5% [231-236] (LE: 3). The use of Doppler US may reduce the number of patients with acute scrotum undergoing scrotal exploration, but it is operator-dependent and can be difficult to perform in pre-pubertal patients [233, 237]. It may also show a misleading arterial flow in the early phases of torsion and in partial or intermittent torsion. Of key importance, persistent arterial flow does not exclude testicular torsion. In a multicentre study of 208 boys with torsion of the testis, 24% had normal or increased testicular vascularisation [233]. A comparison with the other side should always be done.

Better results were reported using high-resolution US (HRUS) for direct visualisation of the spermatic cord twist with a sensitivity of 97.3% and specificity of 99% [233, 238] (LE: 2). A so-called positive whirlpool sign (the presence of a spiral-like pattern), has a pooled sensitivity and specificity of 0.73 (95% CI:, 0.65-0.79) and 0.99 (95% CI:, 0.92-0.99), respectively, and may be viewed as a definitive sign for testicular torsion. But its role in neonates is limited [239].

Scintigraphy and, more recently, dynamic contrast-enhanced subtraction MRI of the scrotum also provide a comparable sensitivity and specificity to US [240-243]. These investigations may be used when diagnosis is less likely and if torsion of the testis still cannot be excluded from history and physical examination. This should be done without inordinate delays for emergency intervention [229].

The diagnosis of acute epididymitis in boys is mainly based on clinical judgement and adjunctive investigation. However, it should be remembered that findings of secondary inflammatory changes in the absence of evidence of an extra-testicular nodule by Doppler US might suggest an erroneous diagnosis of epididymitis in children with torsion of the appendix testes [244]. Pre-pubertal boys with acute epididymitis have an incidence of underlying urogenital anomalies of 25-27.6%. Complete urological evaluation in all children with acute epididymitis is still debatable [199, 222, 224].

*3.5.3 **Management***

3.5.3.1 Epididymitis

In pre-pubertal boys, the aetiology is usually unclear, with an underlying pathology in about 25%. A urine culture is usually negative, and unlike in older boys, a sexually transmitted disease is very rare.

Antibiotic treatment, although often started, is not indicated in most cases unless urinalysis and urine culture show a bacterial infection [224, 245]. Epididymitis is usually self-limiting and with supportive therapy (i.e. minimal physical activity and analgesics) heals without any sequelae (LE: 3). However, bacterial epididymitis can be complicated by abscess or necrotic testis and surgical exploration is required [246].

3.5.3.2 Testicular torsion

Manual detorsion of the testis is done without anaesthesia, and should be attempted in all patients if possible, because it is associated with improved surgical salvage rates [247]. It should initially be done by outward rotation of the testis - like opening a book -, unless the pain increases or if there is obvious resistance. Success is defined as the immediate relief of all symptoms and normal findings at physical examination [248] (LE: 3). Doppler US may be used for guidance [249]. Bilateral orchiopexy is still required after successful detorsion. This should not be done as an elective procedure, but rather immediately following detorsion. One study reported residual torsion during exploration in 17 out of 53 patients, including eleven patients who had reported pain relief after manual detorsion [248, 250].

External cooling before exploration may be effective in reducing ischaemia reperfusion injury and preserving the viability of the torsed and the contralateral testis [251]. Medical treatments aimed at limiting such injury remain experimental [252-255].

Torsion of the appendix testis can be managed non-operatively with the use of anti-inflammatory analgesics (LE: 4). During the six-week follow-up, clinically and with US, no testicular atrophy was revealed. Surgical exploration is done in equivocal cases and in patients with persistent pain [236]. Although metachronous torsion of the appendix testis may occur in up to 8.5%, it is not necessary to explore the contralateral side, given the benign nature ot the problem. Besides it has been demonstrated that the NNT is 24 [256].

3.5.3.3 Surgical treatment

Testicular torsion is an urgent condition which requires prompt surgical treatment. The two most important determinants of early salvage rate of the testis are the time between onset of symptoms and detorsion, and the degree of cord twisting [257]. Severe testicular atrophy occurred after torsion for as little as four hours when the turn was > 360°. In cases of incomplete torsion (180-360°), with symptom duration up to twelve hours, no atrophy was observed. However, a necrotic or severely atrophied testis was found in all cases of torsion > 360° and symptom duration > 24 hours [258].

Early surgical intervention with detorsion (mean torsion time less than thirteen hours) was found to preserve fertility [259]. Urgent surgical exploration is mandatory in all cases of testicular torsion within 24 hours of symptom onset. In patients with testicular torsion > 24 hours, exploration may be performed as a semi-elective exploration procedure [257, 258] (LE: 3), unless there is a clear history of torsion-detorsion in which urgent exploration should still be considered. In case of prolonged torsion (> 24 hours) it is still subject to debate whether the surgically detorsed testis should be preserved. An alternative to detorsion and fixation may be to perform orchiectomy. A study found that sperm quality was preserved after both orchiectomy and orchidopexy in comparison to normal control men, although orchiectomy resulted in better sperm morphology [260] Incision of the tunica albuginea with tunica vaginalis graft to prevent or treat compartment syndrome has also been suggested [261].

In neonates with signs of testicular torsion at birth the duration of symptoms will not be clear. The decision to perform surgical exploration should be weighed against the general condition of the child. In this age group the operation can safely be done under spinal anesthesia. New onset of symptoms of testicular torsion in neonates should be considered a surgical emergency similar to older boys.

During exploration, fixation of the contralateral testis is also performed. It is good clinical practice to also perform fixation of the contralateral testis in prenatal and neonatal torsion, although there is no literature to support this, and to remove an atrophied testicle [262]. Recurrence after orchidopexy is rare (4.5%) and may occur several years later. There is no consensus recommendation about the preferred type of fixation and suture material [263].

*3.5.4 **Follow-up***

Patients require follow-up mainly for fertility issues and hormonal consequences. Despite timely and adequate detorsion and fixation of the testicle, up to half of the patients may develop testicular atrophy, even when intraoperatively assessed as viable, and should be counselled accordingly [264, 265].

3.5.4.1 Fertility

The results vary and are conflicting. In one study, unilateral torsion of the testis seriously intervened with subsequent spermatogenesis in about 50% of the patients and produced borderline impairment in another 20% [242]. Although, 30% of affected testicles with mumps orchitis show a degree of atrophy, long-term outcome in terms of fertility is not conclusive [266].

A recent study showed a normal pregnancy rate after unilateral testicular torsion, with no difference between the patients undergoing orchidopexy and those after orchidectomy [267].

3.5.4.2 Subfertility

Subfertility is found in 36-39% of patients after torsion. Semen analysis may be normal in only 5-50% in long-term follow-up [257]. Early surgical intervention (mean torsion time less than thirteen hours) with detorsion was found to preserve fertility, but a prolonged torsion period (mean 70 hours) followed by orchiectomy jeopardised fertility [259].

Subfertility and infertility are consequences of direct injury to the testis after the torsion. This is caused by the cut-off of blood supply, but also by post-ischaemia-reperfusion injury that is caused after the detorsion when oxygen-derived free radicals are rapidly circulated within the testicular parenchyma [257].

3.5.4.3 Androgen levels

Even though the levels of FSH, luteinising hormone (LH) and testosterone are higher in patients after testicular torsion compared to normal controls, endocrine testicular function remains in the normal range after testicular torsion [260].

3.5.4.4 Unanswered questions

Although testicular torsion is a common problem, the mechanism of neonatal and prenatal torsion is still not exactly known, as well as whether fixation of the contralateral testicle in these cases is really necessary. The influence of an atrophied testicle on fertility is also unclear.

Summary of evidence	**LE**
Diagnosis of testicular torsion is based on presentation and physical exam.	
Doppler US is an effective imaging tool to evaluate acute scrotum and comparable to scintigraphy and dynamic contrast-enhanced subtraction MRI.	2a
Neonates with acute scrotum should be treated as surgical emergencies.	3

Recommendations	**Strength rating**
Testicular torsion is a paediatric urological emergency and requires immediate treatment.	Strong
In neonates with testicular torsion perform orchidopexy of the contralateral testicle. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	Weak
Base the clinical decision on physical examination. The use of Doppler ultrasound to evaluate acute scrotum is useful, but this should not delay the intervention.	Strong
Manage torsion of the appendix testis conservatively. Perform surgical exploration in equivocal cases and in patients with persistent pain.	Strong
Perform urgent surgical exploration in all cases of testicular torsion within 24 hours of symptom onset. In prenatal torsion the timing of surgery is usually dictated by clinical findings.	Strong

3.6 Hypospadias

*3.6.1 **Epidemiology, aetiology and pathophysiology***

3.6.1.1 Epidemiology

The total prevalence of hypospadias in Europe is 18.6 new cases per 10,000 births (5.1-36.8) according to the recent EUROCAT registry-based study. This incidence was stable over the period of 2001 to 2010 [268, 269]. The mean worldwide prevalence of hypospadias according to an extended systematic literature review varies: Europe 19.9 (range: 1-464), North America 34.2 (6-129.8), South America 5.2 (2.8-110), Asia 0.6-69, Africa 5.9 (1.9-110), and Australia 17.1-34.8. There are conflicting data on the recent trends of prevalence – different trends in Europe and an increasing trend in the USA [270, 271].

*3.6.2 **Risk factors***

Risk factors associated with hypospadias are likely to be genetic, placental and/or environmental [268, 269] (LE: 2b). Interactions between genetic and environmental factors may help explain non-replication in genetic studies of hypospadias. Single nucleotide polymorphisms seemed to influence hypospadias risk only in exposed cases [269, 272] (LE: 2b).

- An additional family member with hypospadias is found in 7% of families, but this is more predominant in anterior and middle forms [272-275].
- Endocrine disorders can be detected in rare cases.
- Babies with a low birth weight have a higher risk of hypospadias [272-275].
- Over the last 25 years, a significant increase in the incidence of hypospadias has been found.
- Endocrines disruptors are one component of a multi-factorial model for hypospadias.
- The use of oral contraceptives prior to pregnancy has not been associated with an increased risk of hypospadias in offspring, but their use after conception increased the risk of middle and posterior hypospadias [273-276] (LE: 2a).

*3.6.3 **Classification systems***

Hypospadias are usually classified based on the anatomical location of the proximally displaced urethral orifice:

- distal-anterior hypospadias (located on the glans or distal shaft of the penis and the most commo type of hypospadias);
- intermediate-middle (penile);
- proximal-posterior (penoscrotal, scrotal, perineal).

The pathology may be different after skin release and should be reclassified accordingly. Anatomical location of the meatus may not always be enough to explain the severity and the complex nature of this pathology. Therefore, a simple classification related to severity of the problem, which considers penile length, glans size, shape, urethral plate quality and penile curvature is commonly used. In that classification there are two types: mild hypospadias (glanular or penile isolated hypospadias without associated chordee, micropenis or scrotal anomaly); and severe hypospadias (penoscrotal, perineal hypospadias with associated chordee and scrotal anomalies).

*3.6.4 **Diagnostic evaluation***

Most hypospadias patients are easily diagnosed at birth (except for the megameatus intact prepuce variant which can only be seen after retraction of foreskin). Diagnosis includes a description of the local findings:

- position, shape and width of the orifice;
- presence of atretic urethra and division of corpus spongiosum;
- appearance of the preputial hood and scrotum;
- size of the penis;
- curvature of the penis on erection.

The diagnostic evaluation also includes an assessment of associated anomalies, which are:

- cryptorchidism (in up to 10% of cases of hypospadias);
- open processus vaginalis or inguinal hernia (in 9-15%).

Severe hypospadias with unilaterally or bilaterally impalpable testis, or with ambiguous genitalia, requires a complete genetic and endocrine work-up immediately after birth to exclude DSD, especially congenital adrenal hyperplasia. Urine trickling and ballooning of the urethra requires exclusion of meatal stenosis. The relationship between the severity of the hypospadias and associated anomalies of the upper or lower urinary tract were not confirmed [277] (LE: 3).

3.6.5 ***Management***

3.6.5.1 Indication for reconstruction and therapeutic objectives

Differentiation between functionally necessary and aesthetically feasible operative procedures is important for therapeutic decision making.

The indications for surgery are:

- proximally located (ectopic) meatus causing ventrally deflected or spraying urinary stream;
- meatal stenosis;
- anterior curvature of the penis;
- cleft glans;
- rotated penis with abnormal cutaneous raphe;
- preputial hood;
- penoscrotal transposition;
- split scrotum.

Physical examination should check all anatomic components of the penis and evaluate the degree and nature of abnormality in each component. The examination should evaluate location of the meatus, the degree of proximal spongiosal hypoplasia, presence and degree of penile curvature, width and depth of the urethral plate, size of the glans, degree of ventral skin deficiency, availability of the foreskin and scrotal abnormalities like penoscrotal transposition and bifid scrotum.

As all surgical procedures carry the risk of complications, thorough pre-operative counselling of the caregiver is crucial.

To achieve an overall acceptable functional and cosmetic outcome, the penile curvature must be corrected and a neo-urethra of an adequate size with opening on the glans formed with proper skin coverage of the penile shaft [278] (LE: 4) (Figure 3). The use of magnifying spectacles and fine synthetic absorbable suture materials (6.0-7.0) are required. As in any penile surgery, exceptional prudence should be adopted with the use of cautery. Bipolar cautery is recommended. Knowledge of a variety of surgical reconstructive techniques, wound care and post-operative treatment are essential for a satisfactory outcome.

3.6.5.2 Pre-operative hormonal treatment

There is a lack of high-quality evidence to support that pre-operative hormonal treatment with androgen stimulation improves surgical outcomes. Yet, this treatment in the form of systemic testosterone, topical testosterone, and derivatives like dihydrotestosterone (DHT) and hCG are commonly being used to increase glans size pre-operatively to allow better tubularisation of the urethral plate and decrease the incidence of glans dehiscence. This treatment is usually limited to patients with proximal hypospadias, a small appearing penis, reduced glans circumference or reduced urethral plate [276, 279, 280]. Studies have shown that it leads to significant enlargement of the glans and shaft of the penis (LE: 1b) [281, 282].

Moderate quality evidence from three randomised studies demonstrate significantly lower rates of urethracutaneous fistulae and re-operation rates in patients who received pre-operative hormonal treatment [283].

Pre-operative testosterone administration is most often well tolerated. Transient side effects on child´s behaviour, increased genital pigmentation, appearance of pubic hair, penile skin irritation and redness, increased erections and peri-operative bleeding have been reported, but no persistent side effects related to hormonal stimulation have been reported in the literature. There is also no evidence about possible effects on bone maturation [280, 283, 284].

There are concerns regarding the negative impacts of testosterone on wound-healing and increased bleeding during surgery. Cessation of therapy is recommended one or two months prior to surgery to avoid adverse effects during or after surgery [285].

3.6.5.3 Age at surgery

The age at surgery for primary hypospadias repair is usually 6-18 (24) months [278, 286, 287] (LE: 3). Age at surgery is not a risk factor for urethroplasty complication in pre-pubertal tubularised incised plate urethroplasty (TIP) repair [286] (LE: 2b). Complication rate after primary TIP repair was 2.5 times higher in adults than in the paediatric group according to a recent prospective controlled study [288] (LE: 2a).

3.6.5.4 Penile curvature

If present, penile curvature is often released by degloving the penis (skin chordee) and by excision of the connective tissue of the genuine chordee on the ventral aspect of the penis in up to 70% [289]. The urethral plate has well vascularised connective tissue and does not cause curvature in most cases [290, 291]. The residual curvature is caused by corporeal disproportion and requires straightening of the penis, mostly using dorsal midline plication or orthoplasty (modification of the Nesbit plication with or without elevation of the neurovascular bundle). In more severe curvature (> 45°), which is often combined with a short urethral plate requiring transection, ventral penile lengthening is recommended to prevent shortening of the penis. This consists of a ventral transverse incision of the tunica albuginea extending from the 3 to 9 o´clock position patched with tunica vaginalis flap or graft, or in several short ventral corporotomies without grafting (LE: 2b) [292]. After the ventral lengthening, a shorter dorsal midline plication is usually added.

According to a retrospective study, dorsal plication remained significantly associated with recurrent ventral curvature independently of the other factors. Ventral corporeal grafting for severe penile curvature gives good long-term results and safety profiles for erectile function [293] (LE: 2b).

3.6.5.5 Urethral reconstruction

The mainstay of hypospadias repair is preservation of the well-vascularised urethral plate and its use for urethral reconstruction has become standard practice in hypospadias repair [291]. Mobilisation of the corpus spongiosum/urethral plate and the bulbar urethra decreases the need for urethral plate transection [292] (LE: 2b).

If the urethral plate is wide, it can be tubularised following the Thiersch-Duplay technique. If the plate is too narrow to be simply tubularised, it is recommended relaxing the plate by a midline incision and its subsequent tubularisation according to the Snodgrass-Orkiszewski TIP technique. This technique has become the treatment of choice in distal- and mid-penile hypospadias [294-297]. If the incision of the plate is deep, it is recommended to cover the raw surface with inner preputial (or buccal) inlay graft in primary and secondary repairs [298]. This also enables extension of the incision beyond the end of the plate to prevent meatal stenosis [299, 300] (LE: 2a).

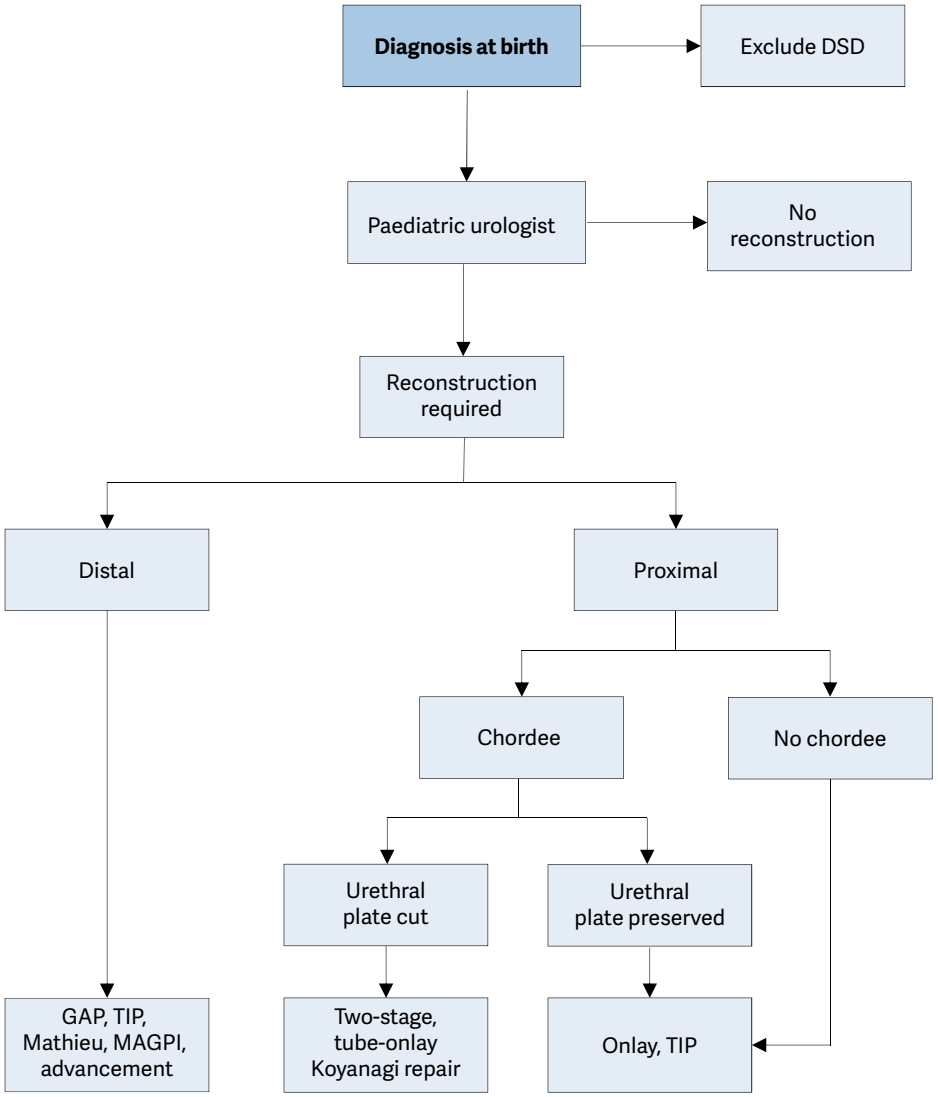
For distal forms of hypospadias, a range of other techniques is available (e.g. Mathieu, urethral advancement) [301] (LE: 2b). The TIP technique has become an option for proximal hypospadias as well [294-297, 302]. However, urethral plate elevation and urethral mobilisation should not be combined with TIP repair because it results in focal devascularisation of the neo-urethra with symptomatic stricture development [303] (LE: 2b). The onlay technique using a preputial island flap is a standard repair, preferred in proximal hypospadias, if a plate is unhealthy or too narrow [289]. An onlay preputial graft is an option for single-stage repair [304] (LE: 2b).

If the continuity of the urethral plate cannot be preserved, single or two-stage repairs are used. For the former, a modification of the tubularised flap (Duckett tube), such as a tube-onlay or an inlay-onlay flap, or onlay flap on albuginea are used to prevent urethral stricture [305-307] (LE: 3); alternatively the Koyanagi-Hayashi technique is used [308-311]. The two-stage procedure has become preferable over the past few years because of lower recurrence of ventral curvature and more favourable results with variable long-term complication rates [300, 305, 312-316].

3.6.5.6 Re-do hypospadias repairs

For re-do hypospadias repairs, no definitive guidelines can be given. All the above-mentioned procedures are used in different ways and are often modified according to the individual findings and needs of the patient.

Figure 3: Algorithm for the management of hypospadias



DSD = disorders of sex development; TIP = tubularised incised plate urethroplasty; MAGPI = meatal advancement and glanuloplasty incorporated.

3.6.5.7 Penile reconstruction following formation of the neo-urethra

Following formation of the neo-urethra, the procedure is completed by glansplasty and by reconstruction of the penile skin. If there is a shortage of skin covering, the preputial double-face technique or placement of the suture line into the scrotum according to Cecil-Michalowski is used. In countries where circumcision is not routinely performed, preputial reconstruction can be considered. Preputial reconstruction carries a risk of specific complications but does not seem to increase the risk of urethroplasty complications [317]. In TIP repair, the use of a preputial dartos flap reduces the fistula rate [294, 295] (LE: 2b).

3.6.5.8 Urine drainage and wound dressing

Urine is drained transurethrally (e.g. dripping stent) or with a suprapubic tube. No drainage after distal hypospadias repair is another option [318, 319]. Circular dressing with slight compression, as well as prophylactic antibiotics during surgery, are established procedures [319] (LE: 4). Post-operative prophylaxis after hypospadias repair has limited benefit and it only reduces the risk of asymptomatic bacteriuria [320-322] (LE: 2b). There is no consensus on duration of stenting and dressing.

3.6.5.9 Outcome

Some studies have tried to determine risk factors for complications after hypospadias repair. An analysis of prospectively collected data found glans size (width < 14 mm), proximal meatal location and re-operation as independent risk factors for urethral complication [319, 323]. Low surgeon volume independently increases the risk of fistula, stricture or diverticulum repair [319, 324] (LE: 3).

A meta-analysis of complication rates of TIP repair found lower complication rates and incidence of re-operations in primary distal repairs (in 4.5%) than in primary proximal repairs (in 12.2%) and in secondary repair (in 23.3%) [294-297, 301, 319]. One should expect a predictable outcome with complication rates below 10% in distal hypospadias (fistula, meatal stenosis, dehiscence, recurrent ventral curvature, and haematoma) [324, 325]. A similar incidence of fistula (3.4-3.6%) can be expected after the Mathieu and TIP repairs of distal hypospadias [302, 326-328].

The complication rates of TIP and onlay repairs of primary severe hypospadias are similar, 24% and 27%, respectively. It is higher in free graft and in preputial island tube urethroplasty [289]. There is no strong evidence to suggest that the use of inlay grafts in TIP repair improves the outcome [329].

The complication rates of single-stage Koyanagi and Hayashi modification repairs go up 61%, according to a comparative study [308, 319]. Staged buccal mucosa graft requires a redo grafting in 13% of patients, after the second stage more than one third of patients have complications, mostly with some degree of graft fibrosis [327, 330]. A recent long-term study on two-stage flap repair showed a complication rate of 68% [319]; another study showed a re-operation rate of 28% [300, 319].

*3.6.6 **Follow-up***

Long-term follow-up is necessary up to adolescence to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, diverticula, glanular dehiscence [331]. Up to half of complications requiring re-operation present after the first year post-operatively [332] (LE: 2b).

Obstructive flow curve is common after hypospadias repair and while most are not clinically significant, long-term follow-up is required [333-336] (LE: 2a). Urine flow is significantly lower in patients after hypospadias surgery, especially in those who had corrected chordee, but without significant association with lower urinary tract symptoms (LUTS) [337] (LE: 2a).

Objective scoring systems have been developed in order to evaluate the results of hypospadias surgery (HOSE) [338] (LE: 2b) and cosmetic appearance (HOPE-Hypospadias Objective Penile Evaluation) [339] (LE: 2a). The Pediatric Penile Perception Score (PPPS) is a reliable instrument to assess penile self-perception in children after hypospadias repair and for appraisal of the surgical result by caregivers and uninvolved urologists [340] (LE: 2a). Cosmetic results were judged more optimistically by surgeons as compared to caregivers using validated tools [341]. Current scoring systems have deficiencies in terms of patient reported outcomes, the long term outcomes and sexual function [342].

Adolescents and adults, who have undergone hypospadias repair in childhood, have a slightly higher rate of dissatisfaction with penile size, especially proximal hypospadias patients, but their sexual behaviour is not different from that of control groups [343, 344] (LE: 2a-b). Another long-term follow-up of men born with hypospadias revealed, in a controlled study, that these patients are less satisfied with penile cosmetic outcome according to all parameters of the PPPS; there was a difference in penile length (9.7 vs. 11.6 cm) and more patients had lower maximum urinary flow. More prominent results were found in proximal hypospadias vs. controls [319, 345].

According to a systematic review of long-term patient satisfaction with cosmetic outcomes [346]:

- patient perception of penile size does not differ greatly from the norm;
- patients approaching puberty have a more negative perception and are more critical about the cosmetic outcomes of surgery;
- patients report high levels of perception of deformity and social embarrassment.

There is a wide range of parameters that are measured to assess outcome after hypospadias surgery in the literature. There is a need for age-specific core outcome set [347].

The majority of identified instruments focused on post-operative cosmetic satisfaction, with only one instrument considering urinary function, and no instruments evaluating sexual function and psychosocial sequelae [348].

3.6.7 *Summary of evidence and recommendations for the management of hypospadias*

Summary of evidence	LE
The suggested age at surgery for primary hypospadias repair is 6-18 (24) months.	3
The therapeutic objectives are to correct the penile curvature, to form a neo-urethra of an adequate size, to bring the new meatus to the tip of the glans, if possible, and to achieve an overall acceptable cosmetic appearance.	4
Androgen stimulation therapy results in increased penile length and glans circumference.	1b
The complication rate is about 10% in distal and 25% in proximal hypospadias one-stage repairs. Higher and variable rates (between 28 and 68%) can occur in two-stage repairs.	3
Sexual functions are usually well preserved but patients report high levels of perception of deformity and social embarrassment.	2b

Recommendations	Strength rating
At birth, differentiate isolated hypospadias from disorders of sex development which are mostly associated with cryptorchidism or micropenis.	Strong
Counsel caregivers on functional indications for surgery, aesthetically feasible operative procedures (psychological, cosmetic indications) and possible complications.	Strong
In children diagnosed with proximal hypospadias and a small appearing penis, reduced glans circumference or reduced urethral plate, pre-operative hormonal androgen stimulation treatment is an option and the body of evidence to accentuate its harms and benefits is inadequate.	Weak
For distal hypospadias, offer Duplay-Thiersch urethroplasty, original and modified tubularised incised plate urethroplasty; use the onlay urethroplasty or two-stage procedures in more severe hypospadias. A treatment algorithm is presented (Figure 3). Correct significant (> 30 degrees) curvature of the penis.	Weak
Ensure long-term follow-up to detect urethral stricture, voiding dysfunctions and recurrent penile curvature, ejaculation disorder, and to evaluate patient´s satisfaction.	Strong
Use validated objective scoring systems to assist in evaluating the functional and cosmetic outcome.	Strong

3.7 Congenital penile curvature

3.7.1 *Epidemiology, aetiology and pathophysiology*

Congenital penile curvature presents penile bending of a normally formed penis due to corporal disproportion. The incidence at birth is 0.6% and congenital penile curvature is caused by asymmetry of the cavernous bodies and an orthotopic meatus [349] because of developmental arrest during embryogenesis [350]. On the other hand, the incidence of clinically significant congenital penile curvature is much lower, because the extent of the curvature and its associated sexual dysfunction varies widely [351]. Most of the cases are ventral deviations (48%), followed by lateral (24%), dorsal (5%), and a combination of ventral and lateral (23%) [352]. Most ventral curvatures are associated with hypospadias due to chordee or ventral dysplasia of cavernous bodies [353]. Similarly, dorsal curvature is mostly associated with exstrophy/epispadias complex. Congenital penile curvature can decrease sexual quality of life in adults and successful repair can restore patients' psychosocial and sexual wellbeing [354].

Curvature > 30° is considered clinically significant; curvature > 60° may interfere with satisfactory sexual intercourse in adulthood (LE: 4). Minor penile curvature may be the result of ventral penile skin deficiency only and should be distinguished from corporal anomalies. For penile curvature associated with hypospadias or epispadias refer to the relevant chapters.

3.7.2 *Diagnostic evaluation*

Penile curvature is frequently not documented until later in childhood since the penis only appears abnormal when erect. Patients are usually concerned with the aesthetic and/or functional aspects of their penis [355]. Besides exact history taking to exclude any possibility of acquired penile curvature (e.g. post-traumatic), a thorough clinical examination is mandatory. In addition, photo documentation of the erect penis clearly showing the curvature from different angles serves as a pre-requisite in pre-operative evaluation [356]. The exact degree of curvature is generally determined at the time of surgery using an artificial erection test.

3.7.3 *Management*

The treatment is surgical, starting with an artificial erection to determine the degree of curvature and to check symmetry after the repair [357]. The ultimate goal of any surgical method used to correct the curvature is to achieve corpora of similar size. Various procedures are in use ranging from simple de-gloving and plication procedures, to corporal rotation, use of free dermal or tunica vaginalis grafts, to complete penile disassembly techniques [358, 359]. Reviews comparing the outcome of Nesbit/modified Nesbit procedures [360] to plication procedures [361] were able to demonstrate that while there is a decreased risk of complications and loss of sensation, it remains unclear whether plication techniques can lead to increased risk of recurrence [362, 363]. Altogether these methods include the risk of post-operative shortening of the penis with an average loss of 2.5 cm in stretched penile length depending on the pre-operative degree of curvature and the type of repair used [364-366].

Recently the non-corporotomy technique has been introduced with promising results enabling correction of any degree of ventral curvature with neither shortening of the penis nor the risk of post-operative erectile dysfunction [367].

3.7.4 *Summary of evidence and recommendations for the management of congenital penile curvature*

Summary of evidence	LE
Isolated congenital penile curvature is relatively uncommon.	2a
Congenital penile curvature is often associated with hypospadias.	2a
Diagnosis is usually made late in childhood.	2a
The penis only appears abnormal when erect.	1b
Congenital penile curvature can cause aesthetic as well as functional sexual problems.	1b
Congenital penile curvature is treated with surgery.	1b
The goal of surgery is to achieve corpora of similar size.	1b

Recommendations	LE	Strength rating
Ensure that a thorough medical history is taken and a full clinical examination done to rule out associated anomalies in boys presenting with congenital curvature.	1a	Strong
Provide photo documentation of the erect penis from different angles as a prerequisite in the pre-operative evaluation.	1b	Strong
Perform surgery after weighing aesthetic as well as functional implications of the curvature.	2b	Weak
At the beginning as well as at the end of surgery, perform artificial erection tests.	2a	Strong

3.8 Varicocele in children and adolescents

3.8.1 *Epidemiology, aetiology and pathophysiology*

Varicocele is defined as an abnormal dilatation of testicular veins in the pampiniformis plexus caused by venous reflux. It is unusual in boys under ten years of age and becomes more frequent at the beginning of puberty. It is found in 14-20% of adolescents, with a similar incidence during adulthood. It appears mostly on the left side (78-93% of cases). Right-sided varicoceles are less common; they are usually noted only when bilateral varicoceles are present and seldom occur as an isolated finding [368-370].

Varicocele develops during accelerated body growth and increased blood flow to the testes, by a mechanism that is not clearly understood. Genetic factors may be present. An anatomic abnormality leading to impaired venous drainage is expressed by the considerable prevalence of the left side condition where the internal spermatic vein drains into the renal vein. Varicocele can induce apoptotic pathways because of heat stress, androgen deprivation and accumulation of toxic materials. Severe damage is found in 20% of adolescents affected, with abnormal findings in 46% of affected adolescents. Histological findings are similar in children or adolescents and in infertile men. In 70% of patients with grade II and III varicocele, left testicular volume loss was found.

Several authors reported on reversal of testicular growth after varicocelectomy in adolescents [371, 372]. An average proportion of catch-up growth of 76.4% (range: 52.6-93.8%) has been found according to a meta-analysis [373] (LE: 2a). However, this may partly be attributable to testicular oedema associated with the division of lymphatic vessels [374] (LE: 2).

In about 20% of adolescents with varicocele, fertility problems will arise [375]. The adverse influence of varicocele increases with time. Improvement in sperm parameters has been demonstrated after adolescent varicocelectomy [376-379] (LE: 1).

3.8.2 ***Classification systems***

Varicocele is classified into 3 grades [380]:

- Grade I - Valsalva positive (palpable at Valsalva manoeuvre only);
- Grade II - palpable (palpable without the Valsalva manoeuvre);
- Grade III - visible (visible at distance).

3.8.3 ***Diagnostic evaluation***

Varicocele is mostly asymptomatic, rarely causing pain. It may be noticed by the patient or caregivers, or discovered by the paediatrician at a routine visit. The diagnosis depends upon the clinical finding of a collection of dilated and tortuous veins in the upright posture; the veins are more pronounced when the patient performs the Valsalva manoeuvre. The size of both testicles should be evaluated during palpation to detect a smaller testis.

Venous reflux into the plexus pampiniformis is diagnosed using Doppler US colour flow mapping in the supine and upright position [381]. Venous reflux detected on US only is classified as subclinical varicocele. To discriminate testicular hypoplasia, the testicular volume is measured by US examination or by orchidometer. In adolescents, a testis that is smaller by > 2 mL or 20% compared to the other testis is considered to be hypoplastic [382] (LE: 2).

Extension of Wilms tumour into the renal vein and inferior vena cava can cause a secondary varicocele. A renal US should be routinely added in pre-pubertal boys and in isolated right varicocele (LE: 4). In order to assess testicular injury in adolescents with varicocele, supranormal FSH and LH responses to the luteinising hormone-releasing hormone (LHRH) stimulation test are considered reliable, because histopathological testicular changes have been found in these patients [378, 383].

3.8.4 ***Management***

There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later. Beneficial effect of pubertal screening and treatment for varicocele regarding chance of paternity has been questioned according to a corresponding questionnaire in adult patients [384] (LE: 4). The recommended indication criteria for varicocelectomy in children and adolescents are [369]:

- varicocele associated with a small testis;
- additional testicular condition affecting fertility;
- bilateral palpable varicocele;
- pathological sperm quality (in older adolescents);
- symptomatic varicocele [384].

Testicular (left + right) volume loss in comparison with normal testes is a promising indication criterion, once the normal values are available [385]. Repair of a large varicocele, causing physical or psychological discomfort, may also be considered. Other varicoceles should be followed-up until a reliable sperm analysis can be performed (LE: 4).

Surgical intervention is based on ligation or occlusion of the internal spermatic veins. Ligation is performed at different levels:

- inguinal (or subinguinal) microsurgical ligation;
- suprainguinal ligation, using open or laparoscopic techniques [386-389].

The advantage of the former is the lower invasiveness of the procedure, while the advantage of the latter is a considerably lower number of veins to be ligated and safety of the incidental division of the internal spermatic at the suprainguinal level.

For surgical ligation, some form of optical magnification (microscopic or laparoscopic) should be used because the internal spermatic artery is 0.5 mm in diameter at the level of the internal ring [386, 388]. The recurrence rate is usually < 10%.

Lymphatic-sparing varicocelectomy is preferred to prevent hydrocele formation and testicular hypertrophy development and to achieve a better testicular function according to the LHRH stimulation test [374, 386, 387, 390] (LE: 2). The methods of choice are subinguinal or inguinal microsurgical (microscopic) repairs, or suprainguinal open or laparoscopic lymphatic-sparing repairs [386, 388, 391, 392]. Intrascrotal application of isosulphan blue was recommended to visualise the lymphatic vessels [393, 394]. In suprainguinal approach, an artery sparing varicocelectomy may not offer any advantage in regards to catch-up growth and is associated with a higher incidence of recurrent varicocele [395, 396].

Angiographic occlusion of the internal spermatic veins also meets the requirements of lymphatic sparing repair. It is based on retrograde or antegrade sclerotisation of the internal spermatic veins [397, 398]. However, although this method is less invasive and may not require general anaesthesia, it is associated with radiation burden, which is less controllable in the antegrade technique [369, 397, 398] (LE: 2).

There is low to moderate level of evidence that radiological or surgical treatment of adolescent varicocele is associated with improved testicular size/growth and sperm concentration - based on current available RCTs. The ultimate effects on fertility and paternity rates are not known [399].

Microsurgical varicocele repair in adolescents with varicocele significantly increases paternity rates and decreases time to conception post-operatively. Patients with varicocele who underwent microsurgical varicocele repair had increased sperm parameters and 3.63 times greater odds of paternity than controls who did not undergo varicocele surgery [400].

The Panel conducted a systematic review and meta-analysis regarding the treatment of varicocele in children and adolescents [401]. Of 1,550 articles identified, 98 articles including 16,130 patients were eligible for inclusion (12 RCTs, 47 NRSs and 39 case series). The key findings are summarised in the following paragraphs:

The meta-analysis of the twelve RCTs revealed that varicocele treatment improved testicular volume (mean difference 1.52 ml, 95% CI 0.73-2.31) and increased total sperm concentration (mean difference 25.54, 95% CI 12.84-38.25) when compared with observation. Lymphatic sparing surgery significantly decreased hydrocele rates (p=0.02) and the OR was 0.08 (95% CI 0.01, 0.67). Due to the lack of RCTs, it was not possible to identify a surgical technique as being superior to the others. It remains unclear whether open surgery or laparoscopy is more successful for varicocele treatment (OR ranged from 0.13 to 2.84).

The success rates of the treatment (disappearance of varicocele) were between 85.1% and 100% whereas the complication rates were between 0% and 29% in the included studies. The most common complication reported was hydrocele. Resolution of pain after treatment was more than 90% in the reported series.

In conclusion, moderate evidence exists on the benefits of varicocele treatment in children and adolescents in terms of testicular volume and sperm concentration. Current evidence does not demonstrate superiority of any of the surgical/interventional techniques regarding treatment success. Lymphatic sparing surgery significantly decreases hydrocele formation. Long-term outcomes, including paternity and fertility, still remain unknown.

*3.8.5 **Summary of evidence and recommendations for the management of varicocele***

Summary of evidence	**LE**
Varicocele becomes more frequent at the onset of puberty and is found in 14-20% of adolescents. Fertility problems are expected in up to 20% of adolescents with a varicocele.	
Pubertal patients with a left grade II and III varicocele have the left testis smaller in up to 70% of cases; in late adolescence the contralateral right testis also becomes smaller.	1b
After adolescent varicocelectomy, left testis catch-up growth and improvement in sperm parameters has been demonstrated.	1a
There is no evidence that treatment of varicocele at paediatric age will offer a better andrological outcome than an operation performed later.	1b
Division of testicular lymphatics leads to hydrocele in up to 40% and to testicular hypertrophy.	1b
Lymphatic sparing surgery significantly decrease hydrocele rates.	1a

Recommendations	**LE**	**Strength rating**
Examine varicocele in the standing position and classify into three grades.	4	Strong
Use scrotal ultrasound to detect venous reflux without Valsalva manoeuvre in the supine and upright position and to discriminate testicular hypoplasia.		Strong
In all pre-pubertal boys with a varicocele and in all isolated right varicoceles perform standard renal ultrasound to exclude a retroperitonal mass.		Strong
Inform caregivers and patients and offer surgery for: • varicocele associated with a persistent small testis (size difference of > 2 mL or 20%); • varicocele associated with additional testicular condition affecting fertility (cryptorchidism, history of torsion, trauma); • varicocele associated with pathological sperm quality (in older adolescents); • symptomatic varicocele.	2	Weak
Use some form of optical magnification (microscopic or laparoscopic magnification) for surgical ligation.	2	Strong

Use lymphatic-sparing varicocelectomy to prevent hydrocele formation and testicular hypertrophy.	1	Strong

3.9 Urinary tract infections in children

*3.9.1 **Epidemiology, aetiology and pathophysiology***

Urinary tract infections (UTIs) represent the most common bacterial infections in children [402-404]. There are several classification systems used to define a UTI. In neonates, the symptoms differ in many aspects from those in infants and children. The prevalence is higher; there is a male predominance; infections caused by other organisms than *Escherichia coli* are more frequent; and there is a higher risk of urosepsis [405, 406].

In children presenting with urinary symptoms a pooled prevalence of UTI was 7.8% (CI: 6.6-8.9) [405]. The incidence varies depending on age and sex. One meta-analysis showed that in children presenting with fever in the first three months of life UTIs were present in 7.5% of girls, 2.4% (CI: 1.4-3.5) of circumcised boys, and 20.1% (CI: 16.8-23.4) of uncircumcised boys [405]. The incidence for boys is highest during the first six months of life (5.3%) and decreases with age to around 2% for the ages 0-6 years. In girls, UTIs are less common during the first six months of life (2%) and incidence increases with age to around 11% for the ages 0-6 years [407].

Associated risk factors for recurrent UTIs include bladder and bowel dysfunction (BBD), vesicoureteral reflux (VUR) and obesity [408-410]. In older children a delay in treatment is more often seen than in younger infants [411]. These risk factors in combination with delay in treatment have been associated with renal scarring [412]. Recurrent febrile UTIs, especially in combination with high-grade VUR, lead to renal scarring [413, 414]. Each new febrile UTI increases the risk of renal scarring with an incidence of renal scarring after the first UTI, of 2.8% (CI:1.2-5.8), 25.7% (CI:12.5-43.3) after the second infection and up to 28.6% (CI:8.4-58.1) after 3 or more febrile UTIs [414].

The leading causative organism for UTIs has been *E. coli*, but other bacteriae have been rising in prevalence. In a large European study *E. Coli* was found in less than 50% of urine cultures. *Klebsiella pneumoniae, Enterobacter spp., Enterococcus spp., Pseudomonas spp., Proteus spp.* and *Candida spp.* are more frequent in nosocomial infections than in community-acquired UTIs, even though, their prevalence has increased outside of the hospital setting [415]. Neonatal UTI is frequently complicated by bacteraemia. In a retrospective study, 12.4% of blood cultures from neonates admitted for UTI were positive for bacteraemia [416], however, it is less frequent in community-acquired than in nosocomial UTI [416, 417].

*3.9.2 **Classification systems***

There are five widely used classification systems according to; site, severity, episode, symptoms and complicating factors. For acute treatment, site and severity are most important.

3.9.2.1 Classification according to site

Lower urinary tract infection (cystitis) is an inflammatory condition of the urinary bladder mucosa with general signs and symptoms including infection, dysuria, frequency, urgency, malodorous urine, enuresis, haematuria, and suprapubic pain.

Upper urinary tract infection (pyelonephritis) is a diffuse pyogenic infection of the renal pelvis and parenchyma. The onset of pyelonephritis is generally abrupt. Clinical signs and symptoms include fever (> 38°C), chills, costovertebral angle or flank pain, and tenderness.

3.9.2.2 Classification according to severity

In a lower UTI, children may have only mild pyrexia; are able to take fluids and oral medication; are only slightly or not dehydrated; and have a good expected level of compliance. When a low level of compliance is expected, such children should be managed as those with severe UTI. In severe UTI, infection is related to the presence of fever of > 39°C, the feeling of being ill, persistent vomiting, and moderate or severe dehydration. Most severe UTIs are upper urinary tract infections.

3.9.2.3 Classification according to episode first/persistent/recurrent/breakthrough

The first UTI may be a sign of anatomical anomalies. Anatomical evaluation is recommended (see below). Recurrent infection can be divided into unresolved and persistent infection.

In unresolved infection, initial therapy is inadequate for elimination of bacterial growth in the urinary tract (inadequate therapy, inadequate antimicrobial urinary concentration [poor renal concentration/ gastrointestinal malabsorption], and infection involving multiple organisms with differing antimicrobial susceptibilities).

Persistent infection is caused by re-emergence of bacteria from a site within the urinary tract coming from a nidus for persistent infection that cannot be eradicated (e.g. infected stones, non-functioning or poorly functioning kidneys/renal segments, ureteral stumps after nephrectomy, necrotic papillae, urachal

cyst, urethral diverticulum, peri-urethral gland, vesicointestinal, rectourethral or vesicovaginal fistulas). The same pathogen is identified in recurrent infections, but episodes of sterile urine may occur during and shortly following antimicrobial treatment.

A breakthough infection in patients under antibacterial prophylaxis is usually caused by resistent bacteria, parental non-compliance and/or severe urogenital anomalies [418, 419].

In re-infection, each episode can be caused by a variety of new infecting organisms, in contrast to bacterial persistence in which the same infecting organism is always isolated. However, the most common general pathogenic species is *E. coli*, which occurs in many different serotypes. Therefore, recurrent *E. coli* UTI does not equate to infection with the same organism.

3.9.2.4 Classification according to symptoms

Children may have typical or atypical symptoms regarding a UTI.

In neonates and infants the most commen symptoms are fever, vomiting, lethargy and/or irritability. Infants and children may have non-specific signs such as poor appetite, failure to thrive, lethargy, irritability, vomiting or diarrhoea. Toilet trained children may report cystitis symptoms along with fever/flank pain.

Asymptomatic bacteriuria indicates attenuation of uropathogenic bacteria by the host, or colonisation of the bladder by non-virulent bacteria that are incapable of activating a symptomatic response (no leukocyturia, no symptoms). Asymptomatic UTI includes leukocyturia but no other symptoms.

Symptomatic UTI, includes irritative voiding symptoms, suprapubic pain (cystitis), fever and malaise (pyelonephritis). Cystitis may represent early recognition of an infection destined to become pyelonephritis, or bacterial growth controlled by a balance of virulence and host response.

3.9.2.5 Classification according to complicating factors

In uncomplicated UTI, infection occurs in a patient with a morphologically and functionally normal upper and lower urinary tract, normal renal function and competent immune system. This category includes mostly isolated or recurrent bacterial cystitis and is usually associated with a narrow spectrum of infecting pathogens that are easily eradicated by a short course of oral antimicrobial agents. Patients can be managed on an outpatient basis, with an emphasis on documenting resolution of bacteriuria, followed by elective evaluation for potential anatomical or functional abnormalities of the urinary tract [420].

A complicated UTI occurs in children with known mechanical or functional pathology of the urinary tract. Mechanical obstruction is commonly due to the presence of posterior urethral valves, strictures or stones, independent of their location. Functional obstruction often results from lower urinary tract dysfunction (LUTD) of either neurogenic or non-neurogenic origin and dilating VUR. Patients with complicated UTI require hospitalisation and parenteral antibiotics. Prompt anatomical evaluation of the urinary tract is critical to exclude the presence of significant abnormalities [421]. If mechanical or functional abnormalities are present, adequate drainage of the infected urinary tract is necessary.

*3.9.3 **Diagnostic evaluation***

3.9.3.1 Medical history

Medical history includes the question of a primary (first) or secondary (recurring) infection; possible malformations of the urinary tract (e.g. pre- or post-natal US screening); prior operation; family history; and, whether there is constipation or presence of lower urinary tract symptoms (LUTS).

3.9.3.2 Clinical signs and symptoms

Neonates with severe UTI can present with non-specific symptoms (failure to thrive, jaundice, hyperexcitability) and without fever. In neonates it is important to rule out a co-existing meningitis [422]. Urinary tract infection is the cause of fever in 4.1-7.5% of children who present to a paediatric clinic [423, 424]. Septic shock is unusual, even with very high fever. Signs of a UTI may be vague and unspecific in small children, but later on, when they are more than two years old, frequent voiding, dysuria and suprapubic, abdominal or lumbar pain can be detected.

3.9.3.3 Physical examination

Physical examination includes a general examination of the throat, lymph nodes, abdomen (constipation, palpable and painful kidney, or palpable bladder), flank, the back (stigmata of spina bifida or sacral agenesis), genitalia (phimosis, labial adhesion, vulvitis, epididymo-orchitis), measurement of body weight and temperature.

3.9.3.4 Urine sampling, analysis and culture

Urine sampling has to be performed before any antimicrobial agent is administered. The technique for obtaining urine for urinalysis as well as culture affects the rate of contamination, which influences interpretation of the results. Especially in early infancy, it can be challenging and depends on the mode of urine sampling [425].

3.9.3.4.1 Urine sampling

Urine must be collected under defined conditions and investigated as soon as possible to confirm or exclude UTI, especially in children with fever. In neonates, infants and non-toilet-trained children, there are four main methods with varying contamination rates and invasiveness to obtain urine:

(1) Plastic bag attached to the cleaned genitalia: Although this technique is most often used in daily practice, contamination rates are high with around 50-60% [426]. It is helpful when the culture results are negative. Also, if the dipstick is negative for both leukocyte esterase and nitrite, or microscopic analysis is negative for both pyuria and bacteriuria, UTI can be excluded without the need for confirmatory culture [427].

(2) Clean-catch urine (CCU) collection: The infant is placed in the lap of a caregiver or member of the nursing staff, who holds a sterile foil bowl underneath the infant's genitalia. The infant is offered oral fluids and urine collection is awaited [428]. Suprapubic tapping alternated with paravertebral lumbar massage can stimulate sponateous voiding [426, 429]. There seems to be a good correlation between the results of urine culture obtained by this method and suprapubic aspiration (SPA), with a false-positive rate of 5% and false-negative rate of 12% [428, 430]; however, the contamination rate is higher for CCU with up to 26% compared to catheterisation 10% and SPA 1% [426, 431]. In one prospective cohort study in infants below the age of six months, the success rate was 49% and the contamination rate 16% with some differences in the culture results between those obtained by CCU and those by more invasive methods [432].

(3) Transurethral bladder catheterisation: is the fastest and safest method to obtain a reliable urine sample fo microscopic and bacteriological evaluation to rule out or to document a UTI in non-toilet trained infants and children.

(4) Suprapubic bladder aspiration: This is the most invasive but also the most sensitive method to obtain an uncontaminated urine sample in this age group [433, 434]. For suprapubic puncture ultrasound imaging should be performed to asses bladder filling.

A two-step procedure where the CCU is screened and a catheter or SPA confirmation of the positive screens is used can lead to a reduction in invasive procedures [426, 431].

In older, toilet-trained children who can void on command, after carefully retracting the foreskin and cleaning the glans penis in boys and spreading the labia and cleaning the peri-urethral area in girls, the use of clean catch, especially midstream urine, could be an acceptable technique for obtaining urine. After cleaning the urethral meatus and perineum with gauze and liquid soap twice, the risk of contamination was reduced from 23.9% (41/171) to 7.8% (14/171) in a randomised trial [435].

3.9.3.4.2 Urinalysis

There are three methods that are commonly used for urinalysis:

(1) Dipsticks: These are appealing because they provide rapid results, do not require microscopy, and are ready to use. Leukocyte esterase (as a surrogate marker for pyuria) and nitrite (which is converted from dietary nitrates by most Gram-negative enteric bacteria in the urine) are the most frequent markers, and are usually combined in a dipstick test. The conversion of dietary nitrates to nitrites by bacteria takes approximately four hours in the bladder [430, 436]. Using only nitrate sticks to screen febrile children < 2 years of age has a too low sensitivity and relevant UTIs can be missed. However, the specificity is high for children at any age [437, 438]. In febrile infants < 90 days old urine dipstick tests using CCU samples can be used for screening for a UTI when nitrites and leukocyte esterase combined are used with a sensitivity of 86% and a specificity of 80% [439].

(2) Microscopy: This is the standard method of assessing pyuria after centrifugation of the urine with a threshold of five white blood cells (WBCs) per high-power field (25 WBC/µL) [440]. In uncentrifuged urine, > 10 WBC/µL has been demonstrated to be sensitive for UTI [441] and this could perform well in clinical situations [442]. However, this is rarely done in an outpatient setting. No significant differences was found between dipsticks and microscopy testing for UTI [438]. A meta-analysis showed, that only microscopy with Gram staining has a higer sensitivity compared to dipsticks [443].

(3) Flow imaging analysis technology: This is being used increasingly to classify particles in uncentrifuged urine specimens [444]. The numbers of WBCs, squamous epithelial cells and red cells correlate well with those found by manual methods [430]. Flow cytometry-based bacterial and leukocyte count analysis when using a cut-off value of 250 bacteria/uL in the presence of leukocyturia has a sensitivity of 0.97 and specificity of 0.91 for diagnosing UTI [445].

3.9.3.4.3 Urine culture

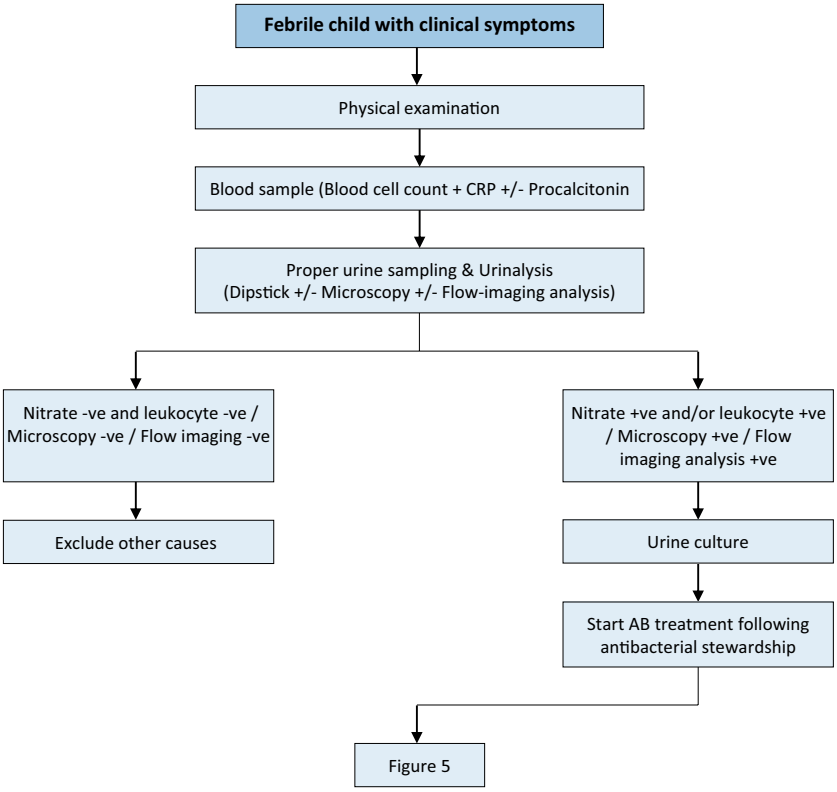
After negative results for dipstick, microscopic or automated urinalysis, urine culture is generally not necessary, especially if there is an alternative source of fever. If the dipstick result is positive, confirmation by urine culture is strongly recommended.

It is unclear what represents a significant UTI. In patients with a severe UTI, ≥ 10^5 cfu/mL can be expected. However, the count can vary and be related to the method of specimen collection, diuresis, and time and temperature of storage until cultivation occurs [406]. Clean-catch urine, midstream and catheterisation urine cultures can be considered positive as 10^3 - 10^4 cfu/mL in a monoculture, and any counts obtained after SPA should be considered as significant. Mixed cultures are indicative of contamination. In febrile children < 4 months of age a cut-off value of 10^3 cfu/mL can be used when clinical and laboratory findings match and a correct sampling method has been used [446].

A negative culture with the presence of pyuria may be due to incomplete antibiotic treatment, urolithiasis, or foreign bodies in the urinary tract, and infections caused by *Mycobacterium tuberculosis* or *Chlamydia trachomatis*.

A flowchart was developed as guidance during the basic diagnostic evaluation and subsequent management of febrile children with clinical symptoms of UTI, Figure 4.

Figure 4: Diagnostic evaluation and subsequent management of a febrile child with clinical symptoms of UTI


Febrile child with clinical symptoms
Physical examination
Blood sample (Blood cell count + CRP +/- Procalcitonin
Proper urine sampling & Urinalysis
(Dipstick +/- Microscopy +/- Flow-imaging analysis)
Nitrate -ve and leukocyte -ve / Microscopy -ve / Flow imaging -ve
Exclude other causes
Nitrate +ve and/or leukocyte +ve / Microscopy +ve / Flow imaging analysis +ve
Urine culture
Start AB treatment following antibacterial stewardship
Figure 5

CRP = C-reactive protein; AB = antibiotic.

3.9.3.5 Imaging

3.9.3.5.1 Ultrasound

Renal and bladder US within 24 hours is advised in infants with febrile UTI to exclude obstruction of the upper and lower urinary tract. Abnormal results are found in 15% of cases, and 1-2% have abnormalities that require prompt action (e.g., additional evaluation, referral or surgery) [427]. When a renal US is performed in all children presenting with a UTI, 7% will have an abnormal US warranting further investigations [447]. The sensitivity to detect high-grade VUR with US was found to be 0.59 (CI: 0.45-0.72) with a specificity of 0.79 (CI: 0.65-0.87) [448]. Renal US should be performed before and after voiding. Post-void residual (PVR) urine should be measured in toilet-trained children to exclude voiding abnormalities as a cause of UTI. Elevated PVR urine volume predicts recurrence of UTIs in toilet-trained children [449]. When peri-renal or psoas abcesses or renal masses are seen on US, it is important to consider xanthogranulomatous pyelonephritis, and subsequent CT imaging is proposed [450].

3.9.3.5.2 Radionuclide scanning/MRI

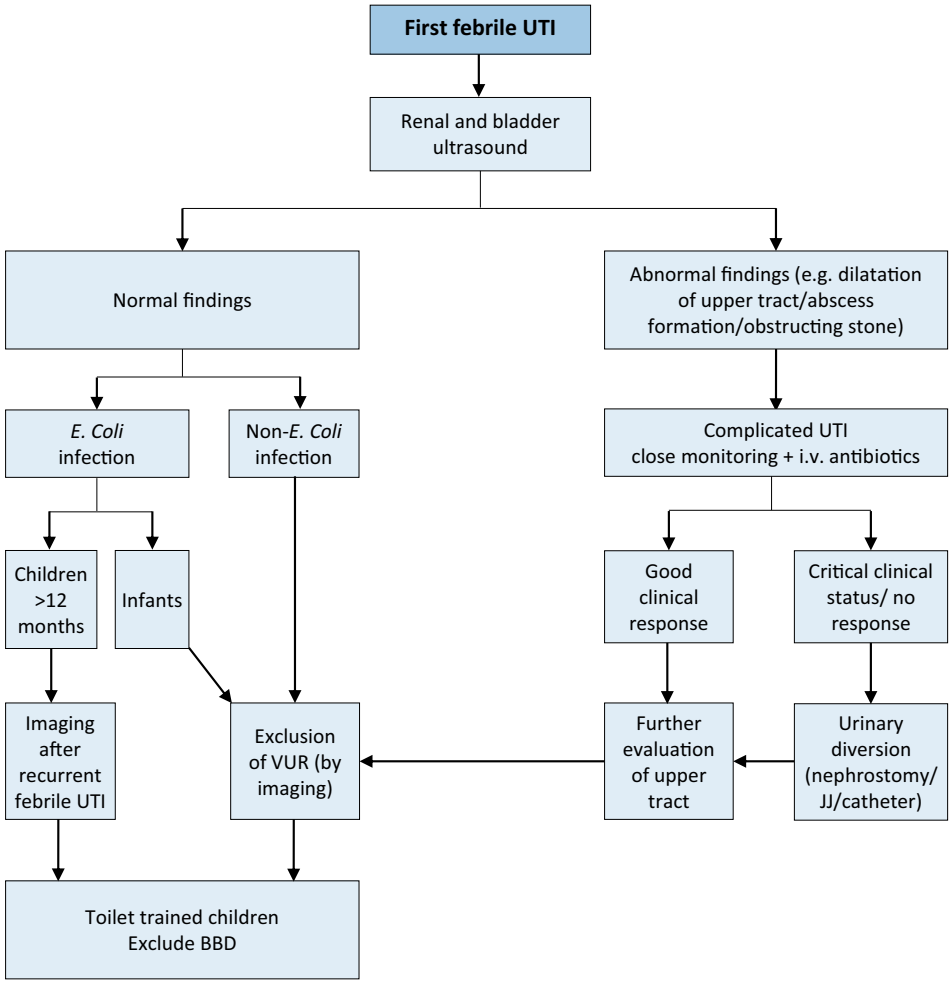
Changes in dimercaptosuccinic acid (DMSA) clearance during acute UTI indicate pyelonephritis or parenchymal damage, correlated with the presence of dilating reflux and the risk of further pyelonephritis episodes, breakthrough infections [451] and future renal scarring. In the acute phase of a febrile UTI (up to four to six weeks), DMSA-scan can demonstrate pyelonephritis by perfusion defects. Renal scars can be detected after three to six months [452]. Diffusion-weighted MRI has shown to accurately diagnose acute pyelonephritis and reveal late renal scars and could be an alternative to DMSA; therefore, avoiding radion burden [453]. The average effective radiation dose of a single DMSA scan was 2.84 (1-12) mSv in one study [454]. These findings are different in neonates. After the first symptomatic, community-acquired UTI, the majority of renal units with VUR grade III or higher had normal early DMSA scanning [455]. The sensitivity of the DMSA scan to detect VUR is 0.75 (CI: 0.67-0.81) with a specificity of 0.48 (CI: 0.38-0.57), and a negative DMSA scan resulting in a very low probability of high-grade VUR [456].

3.9.3.5.3 Voiding cystourethrography/urosonography

The optimum method to exclude or confirm VUR is VCUG. The timing of VCUG does not influence the presence or severity of VUR [457]. Performance of early VCUG in patients with proven sterile urine does not cause any significant morbidity [458]. Using harmonic voiding urosonography may be an alternative to the standard VCUG avoiding radiation [459]. Visulatisation of the urethra may be difficult with this technique.

It is important to diagnose high-grade VUR after the first UTI since this is an important risk for renal scarring. On the other hand, physicians want to avoid unnecessary VCUG investigations at the same time, given its invasive character and radiation burden [447, 460]. Various studies have investigated the risk factors for high-grade VUR and a top down approach is feasible. The most important risk factors for high-grade VUR and subsequent renal scarring are: abnormal renal US, high fever UTI and non-*E. Coli* infections. Different top down strategies with selective VCUG investigations have been proposed [461-465]. Based on these studies we recommend the following updated diagnostic strategy (see Figure 5).

Figure 5: Diagnosis strategy for first febrile UTI


First febrile UTI
Renal and bladder ultrasound
Normal findings
Abnormal findings (e.g. dilatation of upper tract/abscess formation/obstructing stone)
E. Coli infection
Non-E. Coli infection
Complicated UTI close monitoring + i.v. antibiotics
Children >12 months
Infants
Good clinical response
Critical clinical status/ no response
Imaging after recurrent febrile UTI
Exclusion of VUR (by imaging)
Further evaluation of upper tract
Urinary diversion (nephrostomy/ JJ/catheter)
Toilet trained children Exclude BBD

UTI = urinary tract infection; VUR = vesicoureteral reflux; i.v. = intravenous.

3.9.4 ***Management***

3.9.4.1 *Administration route of antibacterial therapy*

The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; and complicated pyelonephritis (e.g. urinary obstruction). As a result of the increased incidence of urosepsis and severe pyelonephritis in newborns and infants aged less than two months, parenteral antibiotic therapy is recommended. Electrolyte disorders with life-threatening hyponatraemia and hyperkalaemia based on pseudohypoaldosteronism can occur in these cases [466, 467].

The choice of agent is also based on local antimicrobial sensitivity patterns, and should later be adjusted according to sensitivity-testing of the isolated uropathogen [430]. Not all available antibiotics are approved by national health authorities, especially in infancy. When recent urinary cultures are available use these sensitivity patterns in the choice for treatment. In children who require intravenuous treatment tobramycin or gentamicin is recommended if there is normal kidney function. When abnormal kidney function is suspected, ceftriaxon or cefotaxime are alternative treatment options. In children who can receive oral treatment without any known resistant urinary cultures, cefixime or amoxicillin-clavulanate are the empirical treatment options [468]. Some studies have demonstrated that once daily parenteral administration of gentamicin or ceftriaxone in a day treatment centre is safe, effective and cost-effective in children with UTI [469-471]. Delaying treatment in children with a febrile UTI for more than 48-72 hours increases the risk of renal scars [412, 472].

3.9.4.2 *Duration of therapy*

Prompt adequate treatment of UTI can prevent the spread of infection and renal scarring. In newborns and young infants with a febrile UTI, up to 20% may have a positive blood culture [416, 421]. Children with bacteremia did not show significant clinical differences with non-bacteremic infants, but did receive longer parental treatment [473]. In late infancy, there are no differences between strategies regarding the incidence of parenchymal scars, as diagnosed with DMSA scan [474]. Outcomes of short courses (one to three days) are inferior to seven to fourteen-day courses [430]. However, a simple cystitis can be treated with three to five days of antibiotics [468]. No significant difference in recurrent UTIs and rehospitalisation was found between seven day parental treatment and longer regimens for bacteremic UTI in younger infants [475]. In young infants a short course of parental treatment with early conversion to oral antibiotics may be considered. The use of exclusively oral therapy with a third-generation cephalosporin (e.g. cefixime or ceftibuten) has been demonstrated to be equivalent to the usual two to four days intravenous therapy followed by oral treatment [476-479]. Similar data have been shown for amoxicillin-clavulanate [480]. If ambulatory therapy is chosen, adequate surveillance, medical supervision and, if necessary, adjustment of therapy must be guaranteed. In the initial phase of therapy, a close ambulant contact to the family is advised [481].

In complicated UTI, uropathogens other than *E. coli*, such as *Proteus mirabilis, Klebsiella spp., Pseudomonas aeruginosa, enterococci* and *staphylococci* are more often the causative pathogens [421]. A temporary urinary diversion (transurethral catheter, suprapubic cystostomy, percutaneous nephrostomy or ureteral stenting) might be required in case of failure of conservative treatment in obstructive uropathy. Children with acute focal bacterial nephritis often present without pyyuria and significant bacteriuria. For the majority of children, the pathogenesis is related to ascending infection due to pre-existing uropathy, especially VUR or urinary obstruction. Initial management consists of broad-spectrum antibiotics with good tissue penetration. A treatment regimen of a total of three weeks with initial intravenous and subsequently oral therapy tailored to the pathogen identified in culture is recommended [482].

3.9.4.3 *Antimicrobial agents*

There is a great difference in the prevalence of antibiotic resistance of uropathogenic *E. coli* in different countries, with increased high resistance patterns in countries outside of the Organisation for Economic Co-operation and Development (OECD) [483]. There are upcoming reports of UTIs caused by extended spectrum ß-lactamase-producing *enterobacteriaceae* (ESBL) in children, with pooled numbers of UTI caused by ESBL producing bacteria of around 14% [484]. Within OECD countries the prevalence of resistance was 53% for ampicillin, 24% for trimethoprim, 8% for co-amoxiclav, 2% for ciproxin and 1% for nitrofurantoin [483]. Several risk factors and determinants for UTIs caused by ESBL and non-*E. Coli* bacteriae have been identified: history of infection, recent hospitalisation, short-term exposure to antiobiotics, and prophylaxis [483, 485, 486]. Overall, oral nitrofurantoin seems to be a good empirical choice in the treatment of cystitis [487].

The choice of antibiotics should be guided by good antibiotic stewardship. It is important to be aware of the local resistance patterns. These are variable between countries and moreover between hospitals. Local antibiotic protocols and web-based recommendations can guide the choice for type of antibiotic therapy. The individual patient's previous urine cultures should also be taken into account in this decision. The daily dosage of antibiotics is depended on the age, weight of the child as well as on renal and liver function.

3.9.4.4 Preventative measures

Recurrent UTIs are problematic because the symptoms are bothersome to children and recurrent febrile UTIs will also result in renal scarring [414]. Therefore, it is important to prevent the incidence of recurrent UTIs.

3.9.4.4.1 Chemoprophylaxis

Chemoprophylaxis is commonly used to prevent UTIs in children. However, with the increasing bacterial resistance numbers, it should be carefully considered which patients should receive antibacterial prophylaxis. The evidence for the use of antibacterial prophylaxis has been conflicting. Its use causes a reduction of the number of recurrent symptomatic UTIs, but long-term use of antibacterial prophylaxis has also been associated with increased microbial resistance [418, 488]. Its use did not reduce newly acquired renal damage in children with first or second UTI [488]. However, when used in patients with anatomic abnormalities of the urinary system a reduction in UTIs and subsequent renal scarring was shown [418, 488]. In children with BBD and VUR, a benefit was seen in the reduction of recurrent UTI with the use of antomicrobial prophylaxis [489, 490] (see also Chapter 3.14 on VUR). For the specific group of patients with incomplete bladder emptying with properly performed clean intermittent catheterisation but still suffering from recurrent UTIs the intravesical application of gentamycin has proven to be effective [491].

Table 1: Drugs for antibacterial prophylaxis*

Substance	Prophylactic dosage (mg/kg bw/d)	Limitations in neonates and infants
Trimethoprim**	2	Not recommended under 6 weeks of age
Trimethoprim Sulfamethoxazole	1-2 10-15	Not recommended under two months of age
Sulfamethoxazole	1-2	Until three months of age
Nitrofurantoin**	1-2	Not recommended under two months of age
Cefaclor	10	No age limitations
Cefixim	2	Preterms and newborns

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*** Substances of first choice are nitrofurantoin and trimethoprim. In exceptional cases, oral cephalosporin can be used.*

3.9.4.4.2 Dietary supplements

Cranberry, mostly as juice, has been shown to prevent UTIs in healthy children, while in children with urogenital abnormalities, cranberries appear to be just as effective as antibiotic prophylaxis [493]. The results for probiotics are somewhat more conflicting, with one systematic review not ruling out any effect [298] and a RCT showing promising results in children with normal urogenital anatomy [494]. A meta-analysis could not demonstrate a beneficial effect, only as an adjuvant to antibiotic prophylaxis [495].

Other supplements of interest were Vitamin A, which showed promising results in preventing renal scarring in children with acute pyelonephritis [496, 497]. The use of Vitamin E could possibly improve the symptoms of UTI [498]. More studies into these supplements are warranted.

3.9.4.4.3 Preputium

A risk reduction of recurrent UTI regarding the preputium has been shown in two studies. When a physiologic phimosis is present in boys with a UTI the use of steroid cream significantly reduced recurrent UTIs [499]. In boys with recurrent UTIs and hydronephrosis present, ten boys would need to be circumcised to prevent one UTI [34].

3.9.4.4.4 Bladder and bowel dysfunction

Bladder and bowel dysfunction is a risk factor for which each child with UTI should be screened upon presentation [409]. Normalisation of micturition disorders or bladder overactivity is important to lower the rate of UTI recurrence. If there are signs of BBD at infection-free intervals, further diagnosis and effective treatment are strongly recommended [490]. Treatment of constipation leads to a decrease in UTI recurrence and a multidisciplinary approach is recommended [409, 489, 490]. Therefore, exclusion of BBD is strongly recommended in any toilet-trained child with febrile and/or recurrent UTI, and it should be treated (For treatment see chapter 3.10 on LUTS).

3.9.4.5 Monitoring of UTI

With successful treatment, urine usually becomes sterile after 24 hours, and leukocyturia normally disappears within three to four days. Normalisation of body temperature can be expected within 24-48 hours after the

start of therapy in 90% of cases. In patients with prolonged fever and failing recovery, treatment-resistant uropathogens or the presence of congenital uropathy or acute urinary obstruction should be considered. Repeated US examination is recommended in these cases.

Procalcitonin (among other laboratory inflammatory parameters such as C-reactive protein and leukocyte count) can be used as reliable serum marker for early prediction of renal parenchymal inflammation [500]. A cut-off value of serum procalcitonin of 1.0 ng/mL has been shown to be predictive of acute pyelonephritis in young children [501]. In patients with febrile UTI, serum electrolytes and blood cell counts should be followed up.

*3.9.5 **Summary of evidence and recommendations for the management of UTI in children***

Summary of evidence	**LE**
Urinary tract infection represents the most common bacterial infection in children less than 2 years of age. The incidence varies depending on age and sex.	1b
Classifications are made according to the site, episode, severity, symptoms and complicating factors. For acute treatment, site and severity are most important.	2b
The number of colony forming units (cfu) in the urine culture can vary, however, any colony count of one specimen indicates a high suspicion for UTI.	2b
Due to increasing resistance numbers good antibiotic stewardship should guide the choice of antibiotics, taking into account local resistance patterns, old urine cultures (when available) and clinical parameters.	2a
Preventive measures against recurrent UTIs include: chemoprophylaxis (oral and intravesical), cranberries, probiotics and Vitamin A and E.	2a
Urinalysis by dipstick yields rapid results, but it should be used with caution. Microscopic investigation is the standard method of assessing pyuria after centrifugation.	2a
During acute UTI both DMSA and diffusion-weighted MRI can confirm pyelonephritis or parenchymal damage.	2a

Recommendations	**LE**	**Strength rating**
Take a medical history, assess clinical signs and symptoms and perform a physical examination to diagnose children suspected of having a urinary tract infection (UTI).	3	Strong
Exclude bladder- and bowel dysfunction in any toilet-trained child with febrile and/or recurrent UTI.	3	Strong
Clean catch urine can be used for screening for UTI. Bladder catheterisation and suprapubic bladder aspiration to collect urine can be used for urine cultures.	2a	Strong
Do not use plastic bags for urine sampling in non-toilet-trained children since it has a high risk of false-positive results.	2a	Strong
Midstream urine is an acceptable technique for toilet-trained children.	2a	Strong
The choice between oral and parenteral therapy should be based on patient age; clinical suspicion of urosepsis; illness severity; refusal of fluids, food and/or oral medication; vomiting; diarrhoea; non-compliance; complicated pyelonephritis.	2a	Strong
Treat febrile UTIs with four to seven day courses of oral or parenteral therapy.	1b	Strong
Treat complicated febrile UTI with broad-spectrum antibiotics.	1b	Strong
Offer long-term antibacterial prophylaxis in case of high susceptibility to UTI and risk of acquired renal damage and lower urinary tract symptoms.	1b	Strong
In selected cases consider dietery supplements as an alternative or add-on preventive measure.	2a	Strong
In infants with febrile UTI use renal and bladder ultrasound to exclude obstruction of the upper and lower urinary tract within 24 hours.	2a	Strong
In infants, exclude vesicoureteric reflux (VUR) after first epidose of febrile UTI with a non-*E. Coli* infection. In children more than one year of age with an *E. Coli* infection, exclude VUR after the second febrile UTI.	2a	Strong

3.10 Day-time lower urinary tract conditions

*3.10.1 **Terminology, classification, epidemiology and pathophysiology***

Urinary incontinence in children may be caused by congenital anatomical or neurologic abnormalities such as ectopic ureter, bladder exstrophy or myelomeningocele (MMC). In many children, however, there is no such obvious cause for the incontinence, and they are referred as having functional bladder problems. The most

recent International Children's Continence Society (ICCS) document suggests using the term day-time lower urinary tract (LUT) conditions to group together all functional bladder problems in children.

Normal storage and emptying of the bladder at a socially accepted place and time is mostly achieved by age three to four. Children with LUT conditions would present with failure to achieve continence (being still wet after the age of four), urgency, weak stream, hesitancy, frequency and accompanied UTIs. Isolated night-time wetting without any day-time symptoms is known as 'enuresis' and considered as a different entity (see chapter 3.11) [502].

As different studies have used varying definitions and criteria, it is difficult to give reliable percentages regarding the incidence of this problem. Reported prevalence ranges widely from 1% to 20% [503-511]. Due to increasing awareness and better access to specialised health care, the prevalence seems to be increasing [512, 513].

Lower urinary tract conditions in children may be due to disturbances of the filling phase, the voiding phase or a combination of both in varying severity. Mainly the conditions are divided into either overactive bladder (OAB) or dysfunctional voiding. They can, of course, coincide and one may even be causative of the other. Dysfunctional bowel emptying may also be part of the clinical problems and BBD is the term used to cover concomitant bladder and bowel disturbances.

Lower urinary tract conditions are considered to be the result of incomplete or delayed maturation of the bladder sphincter complex. The pons is considered to be responsible for detrusor sphincter co-ordination while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition. Therefore overactivity would be the result of delayed maturation of cortical control, while dysfunctional voiding would be the result of non-maturation of the co-ordination. Detrusor overactivity should not be considered as a sole bladder based problem but more a symptom of a centrally located dysfunction affecting bladder, bowel and even mood and behaviour [514].

A link between LUT and behavioural disorders such as ADHD (attention deficit/ hyperactivity disorder) has also been shown [515-517].

3.10.1.1 Filling-phase (storage) dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in OAB, or underactive, as in underactive bladder (UAB). Overactivity of the bladder is the most common problem, seen mostly around five to seven years of age. This may lead to disturbances characterised by urgency, frequency and at times urgency incontinence. Some children habitually postpone micturition leading to voiding postponement. Therefore, holding manoeuvres such as leg crossing and squatting can often be seen in this group. Recurrent UTIs are common and high-pressure state of the bladder can be a cause of VUR. Constipation can be an additional aetiological factor, which needs to be assessed. In children with an underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals. Urinary tract infections, straining to void, constipation and incontinence is common. Incontinence often occurs when the bladder is over-distended in the form of overflow incontinence.

3.10.1.2 Voiding-phase (emptying) dysfunctions

In voiding-phase (emptying), incomplete relaxation or tightening of the sphincteric mechanism and pelvic floor muscles results in staccato voiding pattern (continuous urine flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity) or an interrupted voiding pattern (unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturition in fractions). The general term for this condition is dysfunctional voiding and is associated with elevated bladder pressures and PVRs. Symptoms will vary depending on the severity of inco-ordination between bladder and the sphincter. Staccato voiding is in less severe forms and interrupted voiding and straining is in more severe forms. The co-existence of constipation and LUTD and recurrent UTI is well described [518]. There is no evidence to conclude if bladder problems or bowel problems are the leading cause. The prevalence of constipation in older children varies from 5 to 27%. Approximately 90% of them being functional constipation without an organic cause In children with functinal constipation the prevelance of bladder symptoms have been shown to be as high as 64% [519, 520].

In incomplete emptying, high voiding pressures generated by bladder working against a functional obstruction caused by non-relaxing sphincter may induce not only UTIs but also VUR. It is been shown that LUTD is more significant for the occurrence of UTI than VUR itself [521]. In the majority of children with dysfunctional voiding the recurrent infections disappear following successful treatment, which confirms the hypothesis that

dysfunctional voiding is the main factor responsible for the infections. Spontaneous resolution of VUR may also be seen after successful treatment of dysfunctional voiding.

*3.10.2 **Diagnostic evaluation***

The evaluation of LUT conditions includes medical and voiding history (bladder diaries and structured questionnaires), a physical examination, a urinalysis, and uroflowmetry with PVR. The upper urinary tract (UUT) needs to be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to demonstrate overactivity of the pelvic floor muscles during voiding. Urodynamic studies are usually reserved for patients with therapy resistant dysfunctional voiding and those not responding to treatment who are being considered for invasive treatment [517, 522-525].

In addition to a comprehensive medical history a detailed voiding diary provides documentation of voiding and defecation habits, frequency of micturition, voided volumes, night-time urine output, number and timing of incontinence episodes, and fluid intake. A voiding diary should at least be done for two days, although longer observation periods are preferred. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss. In the paediatric age group, where the history is taken from both the caregivers and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the caregivers and should be specifically requested, using the questionnaire as a checklist. Some symptom scorings have been developed and validated [526, 527]. Although the reliability of questionnaires are limited they are practical in a clinical setting to check the presence of symptoms and have also been shown to be reliable to monitor the response to treatment. History taking should also include assessment of bowel function. For evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [528, 529].

Urinalysis and urinary culture are essential to evaluate for UTI. Since transient voiding symptoms are common in the presence of UTI, exclusion of UTI is essential before further management of symptoms. During clinical examination, genital inspection and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy.

Uroflowmetry with PVR evaluates the emptying ability, while an UUT US screens for (secondary) anatomical changes. A flow rate which reaches its maximum quickly and levels off (‘tower shape’) may be indicative of over-active bladder whereas interrupted or staccato voiding patterns may be seen in dysfunctional voiding. Plateau uroflowmetry patterns are usually seen in anatomic obstruction of flow. A single uroflowmetry test may not always be representative of the clinical situation and multiple uroflowmetry tests, which all give a similar result, are more reliable. Uroflowmetry examination should be done when there is desire to empty the bladder and the voided volume should at least be 50% of the age-expected capacity [(age in years) + 1] x 30 mL for the children. While testing the child in a clinical environment, the impact of stress and mood changes on bladder function should also be taken into account [530, 531].

In the case of treatment failure re-evaluation is warranted and (video)-urodynamic (VUD) studies and neurological evaluation may be considered. Sometimes, there are minor, underlying, urological or neurological problems, which can only be suspected using VUD. In these cases, structured psychological interviews to assess social stress should be added [532] (LE: 1b).

Video-urodynamics may also be used as initial investigational tool in patients with suspicion of reflux. In this case reflux may be observed along with bladder dynamics. In the case of anatomical problems, such as posterior urethral valve (PUV) problems, syringocoeles, congenital obstructive posterior urethral membrane (COPUM) or Moormann’s ring, it may be necessary to perform cystoscopy with treatment. If neuropathic disease is suspected, MRI of the lumbosacral spine and medulla can help to exclude tethered cord, lipoma or other rare conditions.

*3.10.3 **Management***

The treatment of LUTD involves a multimodal approach, involving strategies such as behavioural modification, and anticholinergic medication along with underlying and potentially complicating conditions such as constipation and UTIs.

Behavioural modification, mostly referred to as urotherapy, is a term which covers all non-pharmacological and non-surgical treatment modalities. It includes standardisation of fluid intake, bowel management; timed voiding and basic relaxed voiding education. The child and family are educated about normal bladder function and responses to urgency. Voiding regimens are instituted and UTIs and any constipation are treated. Treatment is aimed at optimising bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding.

Strategies to achieve these goals include:

1. Information and demystification, which includes explanation about normal LUT function and how a particular child deviates from normal function.
2. Instructions about what to do about the problem:
    - Regular voiding habits, sound voiding posture, pelvic floor awareness and training to relax pelvic floor and avoiding holding manoeuvres.
    - Lifestyle advice, regarding fluid intake, prevention of constipation, etc.
    - Registration of symptoms and voiding habits using bladder diaries or frequency-volume charts.
    - Support and encouragement via regular follow-up by the caregiver.

Recurrent UTIs and constipation should also be treated and prevented during the treatment period. In case of combined BBD it is advised to treat the bowel dysfunction first [512] as LUTS may disappear after successful management of bowel dysfunction.

Addition of other strategies, as below, may be needed:

- Pelvic floor muscle awareness practices with repeated sessions of biofeedback visualisation of uroflow curves and/or pelvic floor activity and relaxation.
- Clean intermittent self-catheterisation for large PVR volumes of urine.
- Antimuscarinic drug therapy if detrusor overactivity is present.
- If the bladder neck is associated with increased resistance to voiding, α-blocker drugs may be introduced.

Treatment efficacy can be evaluated by improvement in bladder emptying and resolution of associated symptoms. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described. A high success rate has been described for urotherapy programmes, independent of the components of the programme. However, the evidence level is low as most studies of urotherapy programmes are retrospective and non-controlled [533]. A recent Cochrane analysis found very little evidence that can help to make evidene-based treatment decisions [534].

3.10.3.1 Specific interventions

As well as urotherapy, there are some specific interventions, including physiotherapy (e.g. pelvic floor exercises), biofeedback, alarm therapy and neuromodulation. Although good results with these treatment modalities have been reported, the level of evidence remains low, since only a few RCTs were published [535-541].

A systematic review reports that biofeedback is an effective, non-invasive method of treating dysfunctional voiding, and approximately 80% of children benefited from this treatment. However, most reports were of low level of evidence and studies of more solid design such as RCTs should be conducted [542]. A more recently published multicentre controlled trial of cognitive treatment, placebo, oxybutynin and bladder and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared to standard urotherapy [532] (LE: 1b).

Two RCTs on underactive bladder without neurophatic disease have recently been published. Transcutaneous interferential electrical stimulation and animated biofeedback with pelvic floor exercise have been shown to be effective [543, 544]. In some cases, pharmacotherapy may be added. Some studies on orthosympathicomimetics have been published with a low level of evidence [545].

Overactive bladder is common in the paediatric population. Although a stepwise approach starting with behavioural therapy is advised, antimuscarinic agents remain the mainstay of medical treatment for OAB. Oxybutynin is the most commonly used antimuscarinic in the paediatric population. The response to antimuscarinics varies and many children experience serious side effects. Although there have been reports about the use of tolterodine, fesoterodine, trospium, propiverine, and solifenacin in children, to date, most of them are off-label depending on age and national regulations. A few RCTs have been published, one on tolterodine showed safety but not efficacy [546], while another on propiverine showed both safety and efficacy [547] (LE:1). The recent study on solifenacin showed its efficacy with side effects like constipation and electrocardiogram changes [548].

The difference in results is probably due to study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although α-blocking agents are used occasionally, an RCT showed no benefit [549]. Botulinum toxin injection seems promising, but can only be used off-label [550].

A meta-analysis reports that neuromodulation therapy may lead to better partial improvement of nonneurogenic OAB; however, it may not render a definitive complete response. Office-based neuromodulation seems more efficacious than self-administered neuromodulation [551]. These new treatment modalities can only be recommended for standard therapy-resistant cases [552]. Despite early successful treatment, there is evidence that there is a high recurrence rate of symptoms in the long term which necessitates long-term follow-up [553]. In addition, many patients may present later in adulthood with different forms of LUTD [554].

*3.10.4 **Summary of evidence and recommendations for the management of day-time lower urinary tract conditions***

Summary of evidence	LE
The term 'bladder bowel dysfunction' should be used rather than 'dysfunctional elimination syndrome and voiding dysfunction'.	4
Day-time LUTS has a high prevalence (1% to 20%).	2

Recommendations	LE	Strength rating
Use two day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits and response to treatment.	2	Strong
Use a stepwise approach, starting with the least invasive treatment in managing day-time lower urinary tract dysfunction in children.	4	Weak
Initially offer urotherapy involving bladder rehabilitation and bowel management.	2	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	2	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second line therapy in overactive bladder.	1	Strong
Use antibiotic prophylaxis if there are recurrent infections.	2	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics MRI of lumbosacral spine and other diagnostic modalities, guiding to off-label treatment which should only be offered in highly experienced centres.	3	Weak

3.11 Monosymptomatic nocturnal enuresis - bedwetting

3.11.1 Epidemiology, aetiology and pathophysiology

Monosymptomatic nocturnal enuresis (NE), also known as bedwetting, is defined as an intermittent nocturnal incontinence. It is a relatively frequent symptom in children, 5-10% at seven years of age and 1–2% in adolescents. There is a gender difference in the incidence: two boys to one girl at any age [555]. With a spontaneous yearly resolution rate of 15% (at any age), it is considered as a relatively benign condition [530, 556]. Seven out of 100 seven-year-old bedwetting children will continue to wet their bed into adulthood. Nocturnal enuresis is considered primary when a child has not yet had a prolonged period of being dry (six months). The term "secondary NE" is used when a child or adult begins wetting again after having stayed dry.

Non-monosymptomatic NE is defined as the condition of NE in association with day-time lower urinary tracts symptoms (LUTS, recurrent UTIs and/or bowel dysfunction) [556, 557]. The presence of constipation has a negative association with bladder capacity [558].

Nocturnal enuresis has significant secondary stressful, emotional and social consequences for the child and their caregivers. A lower quality of life has been reported for children with NE compared to controls and NE can influence relationships with friends and family [559-562]. Therefore, treatment is advised from the age of six to seven years onwards considering mental status, family expectations, social issues, and cultural background.

There is a clear hereditary factor in NE. If none of the parents or their immediate relatives has suffered from bedwetting, the child has a 15% chance of wetting its bed. If one of the parents, or their immediate relatives have suffered from bedwetting, the chance of bedwetting increases to 44%, and if both parents have a positive history the chance increases to 77%. However, from a genetic point of view, enuresis is a complex and heterogeneous disorder. Loci have been described on chromosomes 12, 13 and 22 [557].

Children with NE are considered deep but poor sleepers due to high arousal thresholds and frequently disturbed sleep. High arousal threshold is the most important pathophysiological factor in the aetiology of NE: the child does not wake up when the bladder is full. Full night polysomnographic recordings support this hypothesis by demonstrating the disruption of children's sleep microstructure [563]. In addition to the high arousal threshold, there needs to be an imbalance between night-time urine output and night-time bladder

capacity [530, 556, 557]. Recently, attention has been given to the chronobiology of micturition in which the existence of a circadian clock in kidney, brain and bladder is postulated [564].

A high incidence of comorbidity and correlation between nocturnal urine production and sleep disordered breathing, such as obstructive sleep apnoea, has been found and investigated [565, 566]. Symptoms such as habitual snoring, apnoeas, excessive sweating at night and mouth breathing in the patient history or via sleep questionnaires, such as the BEARS questionnaire [567], can lead to the detection of sleep disorders and/or adenotonsillar hypertrophy. When present, a consultation with the ENT specialist can be considered [568].

Obesity is associated with a higher incidence of NE and a lower efficacy for treatment [569]. The presence of allergic diseases has been recognised as a risk factor of NE and with a greater risk for more allergic episodes [570-572].

It is important to consider the child's and family's psychological status as primary NE has been associated with psychopathology, such as Attention Deficit Hyperactivity Disorder (ADHD) and depressive symptoms [573, 574]. In children with ADHD symptoms of NE are more severe and it is important to inform the child and the parents about a delayed success rate and higher relapse rate compared to children without ADHD [575].

*3.11.2 **Diagnostic evaluation***

The diagnosis is mainly obtained by history-taking. Focused questions to differentiate monosymptomatic vs. non-monosymptomatic, primary vs. secondary, comorbid factors such as behavioural or psychological problems and sleep disorder breathing, should be asked. In addition, a two-day complete micturition and drinking diary, which records day-time bladder function and drinking habits will further exclude comorbid factors such as LUTS and polydipsia.

Specific attention should be made regarding bowel movements as irregular bowel movements can change the diagnosis from monosymptomatic NE to non-monosymptomatic NE. If constipation or faecal incontinence is found (it is reported in up to 20% of children with NE), it should be treated simultaneously, and the family should be informed that constipation can negatively influence treatment outcomes [576, 577].

The night-time urine production should be registered by weighing the night-time diapers in the morning and adding the first morning voided volume [578]. The night-time urine production should be recorded over (at least) a two-week period to diagnose an eventual differentiation between a high night-time production (more than 130% of the age expected bladder capacity) vs. a night-time OAB.

A physical examination should be performed with special attention to the back of the child (to exclude any neurological problem), the external genitalia and surrounding skin, as well as to the condition of the clothes (wet underwear or encopresis).

Urine analysis is indicated if there is a sudden onset of bedwetting, a suspicion or history of UTIs, or inexplicable polydipsia.

A uroflowmetry and US is indicated only if there is a history of previous urethral or bladder surgery and presence of daytime urinary symptoms. For further evaluation, see Section 3.10 on Day-time LUT conditions.

There is no clinical indication nor use for a functional MRI (fMRI) in the diagnostic of NE. Research is ongoing, however one of the main issues is the fact that the MRI is performed in an awake state, whereas the NE is a solely event during sleep. The use of fMRI in the elucidation of the NE's neuropathological mechanisms has not yet been fruitful [579, 580].

*3.11.3 **Management***

Before introducing any form of possible treatment, it is of utmost importance to explain the bedwetting condition to the child and the caregivers in order to demystify the problem. Parents should be encouraged to seek medical attention for their bedwetting children and be informed that it is known that the quality of life of parents with a child with NE is negatively impaired. Medical providers assisting families with a child must be aware of this fact and therefore guide parents, by explaining that the key role for treating a child with NE is the ability to understand and the co-operation of the child itself [581].

Since the COVID-19 pandemic situation and promotion of virtual contacts between doctors and patients, it has been shown that telemedicine is a good method of closely follow-up and can be used for follow-up after treatment [582].

3.11.3.1 Supportive treatment measures

Initially, supportive measures including normal and regular eating and drinking habits should be reviewed, stressing normal fluid intake during the day and reducing fluid intake in the hours before sleep. Keeping a chart depicting wet and dry nights, also called as basic bladder advice, has not been shown to be successful

in the early treatment of NE [583]. To assure good sleep quality, specifically in children with NE, it is also recommended to limit the use of electronic devices before bedtime [584].

Referral for psychological support should be advised and followed-up for patients with NE and their families, especially if the NE comorbid factor is developmental, attention or learning difficulties, family problems, parental distress and possible punishment of the child are observed. Parental stress levels are higher compared to parents of non-NE children [585] and anger is found to be the most common parental reaction towards NE children [586], this would explain why childhood traumas such as neglect and abuse are more often seen in children with NE [587]. Psychological interventions with parents of NE children were shown to significantly improve their coping mechanisms [588].

3.11.3.2 Wetting alarm treatment

The nocturnal alarm treatment relies on the use of a device that is activated by getting wet. The goal of this therapeutic approach is that the child wakes up by the alarm, which can be acoustic or tactile, either by itself or with the help of a caregiver. Their method of action is to repeat the awakening and therefore change the high arousal to a low arousal threshold, specifically when a status of full bladder is reached. In the most recent Cochrane review (even though the quality of the included studies was low), several studies have shown that alarm treatment will reduce the number of wet nights a week. An alarm treatment has a higher complete response rate and a low relapse rate compared to no treatment at all [589]. In the event of relapse after initial success, one should actively investigate for OAB [590]. The recommended length of therapy with the alarm treatment continues to be uncertain, varying from 8-12 weeks (ICCS) to 16-20 weeks [591].

Regular follow-up will improve the success. It is of utmost importance that the child plays an active role in the alarm treatment, is willing to continue and understand the purpose of the treatment modality.

3.11.3.3 Medical treatment

If the child and the family would like to act on the high night-time urine production and eventual night-time OAB, they should be able and willing to adjust their drinking habits and take either desmopressin or a combination of desmopressin and an anticholinergic drug.

Success rates of 70% can be obtained with Desmopressin , either as tablets (200-400 µg), or as sublingual Desmopressin oral lyophilisate (120-240 µg). A rare side-effect is water intoxication which can be prevented by adequate water intake. The dosage of 120 ug has been shown to be effective and safe [592, 593]. A structured titration increase up to 240 ug has been shown to be effective [594]. Predictive factors for success with Desmopressin have been identified: older children, in children with fewer wet nights and high night-time urine production [595]. Children that show a good response on low-dose Desmopressin are more likely to show a complete response during the maintenance period [596]. When poor responses are seen on Desmopressin be aware of low compliance [597]. Relapse rates can be high after Desmopressin discontinuation [530], it is unclear if structured withdrawal will result in lower relapse rates [598, 599]. A nasal spray is no longer recommended due to the increased risk of overdose [600].

In the event of Desmopressin-resistant treatment for NE or if a suspicion exists for night-time OAB, combination of Desmopressin with anticholinergics is safe and efficient, even after cessation of treatment [601-604]. With night-time OAB a treatment failure to Desmopressin can be explained because of the bladder reservoir dysfunction [605]. There is no indication for monotherapy with an anticholinergic drug [606].
Alarm and Desmopressin treatment have comparable efficacy in achieving >50% reduction in wet nights. Alarms offer superior treatment response (OR: 2.89, 95% CI 1.38 to 6.04) and lower relapse rates (OR: 0.25, 95% CI 0.12 to 0.50) in children [607]. Multimodal treatment can achieve a partial or full response in 80% of children. However, side effects are seen in up to 30% of children [608].

3.11.3.4 Electrical neuromodulation

Several systematic reviews and randomized trials have documented potential benefits of electrical neural stimulation for NE. However, the quality of the included studies was low and different types of electrical neural stimulation, such as intra-anal stimulation and interferential current stimulation have been included [609-612]. The one RCT that compares transcutaneous electrical nerve stimulation to placebo demonstrates no anti-enuretic effect [613].

3.11.3.5 Complementary treatments:

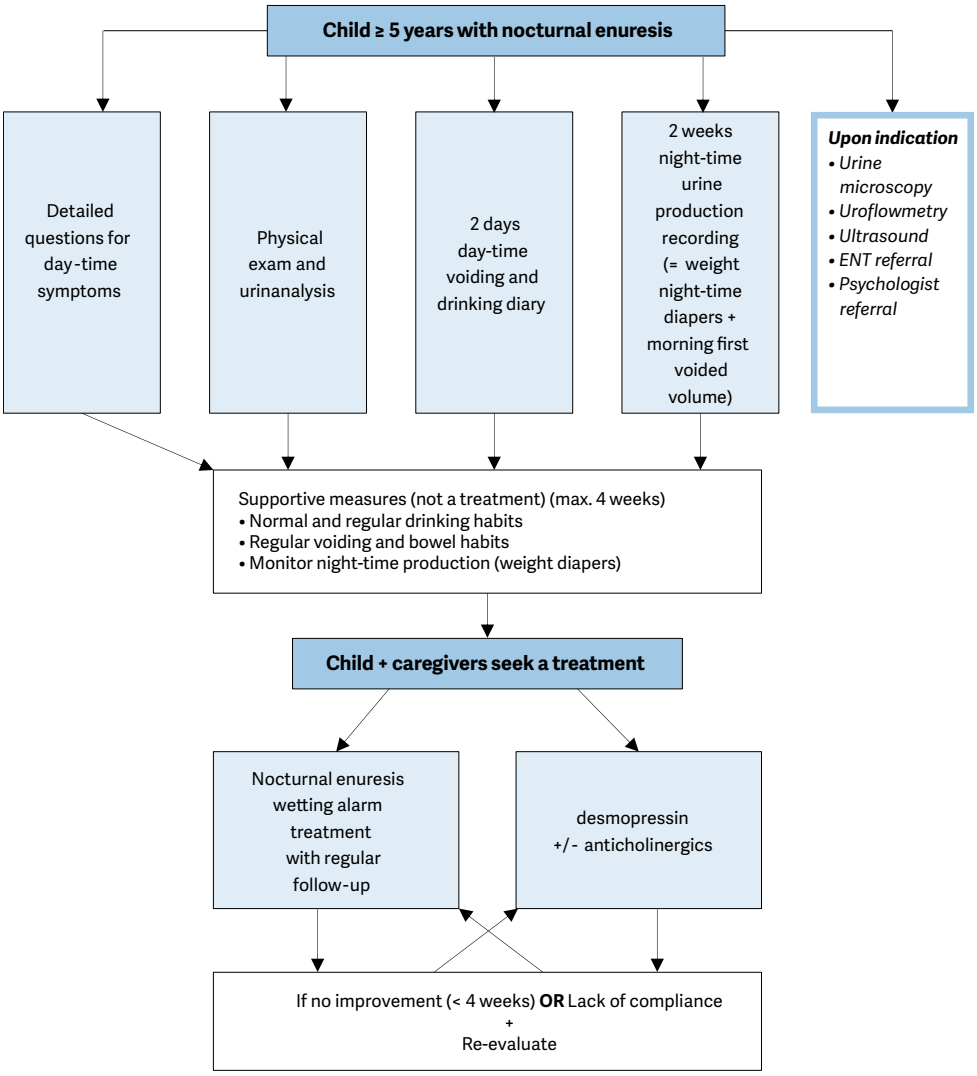
A Cochrane review showed no benefit for treatments such as hypnosis, psychotherapy, acupuncture, chiropractic and medicinal herbs for the treatment of NE [614].

3.11.3.6 Conservative “wait and see” approach

If the child and its family is unable to comply with a treatment, if the treatment options are not possible for the

family situation, and if there is no social pressure, a “wait and see” approach can be chosen. However, in this approach, it is important to emphasise the fact that the child should wear diapers at night to ensure a normal quality of sleep [615]. The success rate of wait and see is 15% per year, independent of age. Figure 6 presents stepwise assessment and management options for NE.

Figure 6: A stepwise assessment and management options for NE


Child ≥ 5 years with nocturnal enuresis
Detailed questions for day-time symptoms
Physical exam and urinanalysis
2 days day-time voiding and drinking diary
2 weeks night-time urine production recording (= weight night-time diapers + morning first voided volume)
Upon indication
• Urine microscopy
• Uroflowmetry
• Ultrasound
• ENT referral
• Psychologist referral
Supportive measures (not a treatment) (max. 4 weeks)
• Normal and regular drinking habits
• Regular voiding and bowel habits
• Monitor night-time production (weight diapers)
Child + caregivers seek a treatment
Nocturnal enuresis wetting alarm treatment with regular follow-up
desmopressin +/- anticholinergics
If no improvement (< 4 weeks) OR Lack of compliance
+
Re-evaluate

ENT = ear, nose and throat.

3.11.4 Summary of evidence and recommendations for the management of monosymptomatic enuresis

Summary of evidence	LE
Chronobiology of micturition, in which the existence of a circadian clock has been proven in kidney, brain and bladder, and disturbances in this chronobiology play a major role in the pathophysiology of enuresis.	1

Recommendations	LE	Strength rating
Do not treat children less than five years of age in whom spontaneous cure is likely, but inform the family about the involuntary nature, the high incidence of spontaneous resolution and the fact that punishment will not help to improve the condition.	2	Strong
Use micturition diaries or questionnaires to exclude day-time symptoms.	2	Strong

Perform a urine test to exclude the presence of infection or potential causes such as diabetes insipidus.	2	Strong
Offer supportive measures in conjunction with other treatment modalities, of which pharmacological and alarm treatment are the two most important.	1	Strong
Offer desmopressin in proven night-time polyuria.	1	Strong
Offer alarm treatment in motivated and compliant families.	1	Strong

3.12 Management of neurogenic bladder

*3.12.1 **Epidemiology, aetiology and pathophysiology***

Neurogenic detrusor-sphincter dysfunction (NDSD) can develop as a result of a lesion at any level in the nervous system. This condition contributes to various forms of LUTD, which may lead to incontinence, UTIs, VUR, and ultimately to renal scarring and renal failure requiring dialysis and/or transplantation. Conservative treatment starting in the first year of life is the first choice, however, surgery may be required at a later stage to establish adequate bladder storage, continence and drainage later on [616]. The main goals of treatment concerning the urinary tract are prevention of UTI's, urinary tract deterioration, achievement of continence at an appropriate age and promoting a good as possible QoL [4, 5]. With regard to the associated bowel dysfunction, stool continence, with evacuation at a social acceptable moment, is another goal as well as education and treatment of disturbance in sexual function. Due to the increased risk of development of latex allergy, latex-free products (e.g., gloves, catheters etc.) should be used from the very beginning whenever possible [617].

Neurogenic bladder in children with myelodysplasia presents with various patterns of Detrusor-Sphincter-Dyssynergia with a wide range of severity [618]. About 12% of neonates with myelodysplasia have no signs of neuro-urological dysfunction at birth [619]. Newborns with myelodysplasia who initially have normal urodynamic studies are at risk for neurological deterioration secondary to spinal cord tethering, especially during the first six years of life. Close follow-up of these children is important for the early diagnosis and timely surgical correction of tethered spinal cord, and for the prevention of progressive urinary tract deterioration [619]. At birth, the majority of patients have normal UUTs, but up to 60% develop upper tract deterioration due to bladder changes, UTI and /or VUR, if not treated properly [620-623]. Even today in a contemporary series around 50% of the patients are incontinent and 15% have an impaired renal function at the age of 29 years [624]. A systematic review concerning the outcome of adult meningomyelocele patients demonstrated that around 37% (8-85%) are continent, 25% have some degree of renal damage and 1.3% end stage renal failure [625]. The term "continence" is used differently in the reports, and the definition of "always dry" was used in only a quarter of the reports [626]. A recent nationwide survey in USA showed, that less than 50% of the adult spina population reported being continent [627], which demonstrates the need for better consulting and lifelong support.

The most common presentation at birth is myelodysplasia. The incidence of neural tube defects in Europe is 9.1 per 10,000 births and has not decreased in recent years, despite longstanding recommendations concerning folic acid supplementations [628]. The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure. Lesions include spina bifida aperta and occulta, meningocele, lipomyelomeningocele, or myelomeningocele. Myelomeningocele is by far the most common defect seen and the most detrimental.

With antenatal screening spina bifida can be diagnosed before birth with the possibility of intrauterine closure of the defect [629, 630]. Traumatic and neoplastic spinal lesions of the cord are less frequent in children but can also cause severe urological problems. Other congenital malformations or acquired diseases can cause a neurogenic bladder, such as total or partial sacral agenesis which can be part of the caudal regression syndrome [631]. In any child presenting with anorectal malformation (ARM) and cloacal malformations, the development of a neurogenic bladder is possible [632]. Patients with cerebral palsy may also present with varying degrees of voiding dysfunction, usually in the form of uninhibited bladder contractions (often due to spasticity of the pelvic floor and sphincter complex) and wetting. Finally, "non-neurogenic neurogenic" bladder dysfunction, such as Hinman or Ochoa syndrome, have been described, in which no neurogenic anomaly can be found, but severe bladder dysfunction as seen in neurogenic bladders is present [633, 634].

*3.12.2 **Classification systems***

As bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion, urodynamic and functional classifications are much more practical for defining LUT pathology and planning treatment in children.

The bladder and sphincter are two units working in harmony to act as a single functional unit. In patients with a neurogenic disorder, the storage and emptying phase of the bladder function can be disturbed. The bladder and sphincter may be either overactive or underactive and present in four different combinations. This classification system is based on urodynamic findings [635-637]:

- Overactive sphincter and overactive bladder.
- Overactive sphincter and underactive bladder.
- Underactive sphincter and overactive bladder.
- Underactive sphincter and underactive bladder.

*3.12.3 **Diagnostic evaluation***

Today several guidelines and timetables are used [638-640]. The Panel advocate proactive management in children with spinal dysraphism. In those with a safe bladder during the first urodynamic investigation, the next urodynamic investigation can be delayed until one year of age [4].

3.12.3.1 History and clinical evaluation

History should include questions on clean intermittent catheterisation (CIC) frequency, urine leakage, bladder capacity, UTI, medication, bowel function as well as changes in neurological status. A thorough clinical evaluation is mandatory including the external genitalia and the back. A two-day diary, recording drinking volume and times as well as CIC intervals, bladder volume and leakage can provide additional information about the efficacy of the treatment.

3.12.3.2 Laboratory and urinalysis

After the first week of life, plasma creatinine level should be obtained, later in life; cystatin level is more accurate [641, 642]. If there is any sign of decreased renal function, physicians should be encouraged to optimize the treatment as much as possible. The criteria for urine analysis are the same as for UTI (refer to Chapter 3.9). However, it is much easier for caregivers or patients to obtain catheter urine in patients who are on CIC. They can also perform a dip stick analysis to screen for UTI at home. (For relevance see Section 3.12.4.5). Albuminuria is an early marker of renal disease also in children with neurogenic bladder [643].

3.12.3.3 Ultrasound

At birth, US of the kidneys and bladder should be performed and then repeated at least annually. If there are any clinical changes in between, another US should be performed. Dilatation of the UUT should be reported according to the classification system of the Society of Foetal Urology [644], including the measurement of caliceal dilatation and anterior posterior diameter of the renal pelvis. Residual urine and bladder wall thickness should also be noted. A dilated ureter behind the bladder should be recorded. Bladder wall thickness has been shown not to be predictive of high pressures in the bladder during voiding and storage and cannot be used as a non-invasive tool to judge the risk for the UUT [645].

3.12.3.4 Urodynamic studies/videourodynamic

Urodynamic studies (UD) are one of the most important diagnostic tools in patients with neurogenic bladders. In newborns with spina bifida aperta), the first UD should be performed after the phase of spinal shock after closure, usually between the second and third months of life [646]. Especially in newborns, performing and interpretation of UD may be difficult, as no normal values exist. After that it should be repeated annually, depending on the clinical situation. During and after puberty bladder capacity, maximum detrusor pressure and detrusor leak point pressure increase significantly [647]. Therefore, during this time, a careful follow-up is mandatory.

3.12.3.4.1 Preparation before urodynamic studies

Before any UD a urine analysis should be undertaken. The first assessment should be done under antibiotic prophylaxis. A Cochrane analysis of nine randomised controlled trials showed, that the administration of prophylactic antibiotics compared to placebo reduced the risk of significant bacteriuria from 12% to 4% after UD studies. However, this was without significant difference for symptomatic UTI (20% vs. 28%), fever or discomfort [648]. If there is significant bacteriuria, antibacterial treatment should be discussed; especially in older patients a single dose may be sufficient [649].

Generally, UD-parameters should include:

- the cystometric capacity;
- the intravesical filling pressure;
- detrusor compliance;
- the intravesical pressure at the moment of voiding or leakage;

- the presence or absence of detrusor overactivity;
- the competence of the internal and external sphincter;
- the degree of synergy of the detrusor and sphincter during voiding;
- the PVR volume.

In infants, information on detrusor filling pressure and the pressure and bladder volume at which the child voids or leaks can be obtained [646]. Detrusor leak point pressure is more accurate than abdominal leak point pressure but keeping the rectal probe in an infant in place can be challenging [646]. Addition of fluoroscopy (video-urodynamic study) will provide information about presence of VUR, at what pressures VUR occurs and the configuration of the bladder neck during filling and leakage or voiding.

3.12.3.4.2 Uroflowmetry

Unlike in children with non-neurogenic voiding dysfunction, uroflowmetry can rarely be used since most affected patients do not void spontaneously. In those with cerebral palsy, non-neurogenic-neurogenic bladder or other neurological conditions allowing active voiding it may be a practical tool. It provides an objective way of assessing the efficiency of voiding, while recording of pelvic floor activity with electromyography (EMG) can be used to evaluate synergy between detrusor and the sphincter. PVR urine volume is measured by US. The main limitation of uroflowmetry is the compliance of the child to follow instructions [650-653].

3.12.3.5 Urodynamic studies

The standards of the ICCS should be applied to UDs in patients with neurogenic bladders and accordingly reported [522, 636]. Natural fill UD in children with neurogenic bladder detects more overactivity compared with diagnoses delivered by conventional UD [654, 655]. It may be an option in patients where the findings in the conventional UD are inconsistent with clinical symptoms and other clinical findings [655].

3.12.3.6 Voiding cystourethrogram

If video-urodynamic equipment is not available, a VCUG with UD is an alternative to confirm or exclude VUR and visualise the LUT including the urethra.

3.12.3.7 Renal scan

DMSA (Technetium Dimercapto-Succinic Acid) Renal scan is the gold standard to evaluate renal parenchyma. In contemporary series, renal scars can be detected in up to 46% as patients get older [656-658]. In a recent study 4 out of 68 children had renal scarring, 3 had a history of febrile UTI and one a vesicoureteral reflux [608]. A positive DMSA-Scan correlates well with hypertension in adulthood, whereas US has a poor correlation with renal scars [658]. Therefore, a DMSA scan as a baseline evaluation in the first year of life is recommended.

3.12.4 ***Management***

The medical care of children with neurogenic bladder requires an on-going multidisciplinary approach. There is some controversy about optimal timing of the management; proactive vs. expectant management [659-661]. Even with a close expectant management e.g. in one series 11 out of 60 need augmentation within a follow-up of 16 years and 7 out of 58 had a decrease in total renal function, which was severe in two [662]. During the treatment it should also be taken into account in spina bifida patients, that QoL is related to urinary incontinence independent of the type and level of spinal dysraphism and the presence or absence of a liquor shunt [663].

Foetal open and endoscopic surgery for meningomyelocele are performed to close the defect as early as possible in order to reduce neurological, orthopaedic and urological problems [664]. In the MOMS-Trial, Brooks *et al*. found no difference between those closed *in utero* vs. those closed after birth concerning the need for CIC [630], but less bladder trabeculation was found in the prenatal surgery group. Mean gestation age (28.3 vs. 35.2) seems to have no initial impact on bladder function in the first few years of life [665]. Two European series showed, that there is a possible benefit of open intrauterine closure on urinary continence showing normal bladder function in up to 33% at least in the first 2-3 years of life [666] [667]. Despite these promising reports [665, 668-670], caregivers need to be aware of the high risk of developing a neurogenic bladder as demonstrated by a Brazilian group [671]. Regular and close follow-up examinations including UD are indicated in all these patients.

3.12.4.1 Early management with intermittent catheterisation

Starting intermittent catheterisation (IC) soon after birth and closure of the defect by the neurosurgeon in all infants has shown to decrease renal complications and the need for later augmentation [672-675]. In infants without any clear sign of outlet obstruction, this may be delayed but only in very selected cases. These infants

should be monitored very closely for UTIs and changes of the urinary tract with US and UD. The early initiation of CIC in the new-born period makes it easier for caregivers to master the procedure and for children to accept it, as they grow older [676, 677]. Up to 90% of patients will perform CIC [678].

A Cochrane review as well as a recent study showed, that there is a lack of evidence to state that the incidence of UTI is affected by use of sterile or clean technique, coated or uncoated catheters, single (sterile) or multiple use (clean) catheters, self-catheterisation or catheterisation by others, or by any other strategy [679-683]. Looking at the microbiological milieu of the catheter, there was a trend for reduced recovery of potentially pathogenic bacteria with the use of hydrophilic catheters. Also, a trend for a higher patient satisfaction with the use of hydrophilic catheters was seen [684]. Based on the current data, it is not possible to state that one catheter type, technique or strategy is better than any other.

3.12.4.2 Medical therapy

Antimuscarinic/anticholinergic medication reduces/prevents detrusor overactivity and lowers intravesical pressure [685, 686]. Effects and side effects depend on the distribution of the M1-M5 receptors [687]. In the bladder, the subtype M2 and M3 are present [686, 688]. Oxybutynin is the most frequently used in children with neurogenic bladder with a success rate of up to 93% [689, 690]. Dose-dependent side-effects (such as dry mouth, facial flushing, blurred vision heat intolerance etc.) limit its use. Intravesical administration gives a significant higher bioavailability due to the circumvention of the intestinal first pass metabolism, as well as possible local influence on C-fiber-related activity and can be responsible for different clinical effect [691, 692].

Intravesical administration should be considered in patients with severe side-effects, as long-term results demonstrated that it was well-tolerated and effective [693, 694]. Transdermal administration also leads to a substantially lower ratio of N-desethyloxybutynin to oxybutynin plasma levels, however, there are treatment-related skin reactions in 12 out of 41 patients [695]. There are some concerns about central anticholinergic adverse effects associated with oxybutynin [696, 697]. A double blinded cross-over trial, as well as a case control study, showed no deleterious effect on children's attention and memory [658, 698]. Tolterodine, solifenacine, fesoterodin, trospium chloride and propiverine and their combinations can also be used in children [699-707].

The oral dosage for oxybutynin is up to 0.2 mg/kg [686] given three times daily. The intravesical dosage can be up to 0.7 mg/kg/daily and transdermal 1.3-3.9 mg/daily. The dosage of the other drugs is: Tolterodine 0.5 – 4 mg/day divided in two doses, Solifenacin 1.25 up to 10 mg per day (single dose), fesoterodine 4-8 mg per day (single dose) Propiverin 0.8 mg/kg/day divided in two dosages and trospium chloride up to 3 times 15 mg starting with 3 times 5 mg. Except for oxybutynin, all other anticholinergic drugs are off-label use, which should be explained to the caregivers.

Early prophylactic treatment with anticholinergics showed a lower rate of renal deterioration as well as a lower rate of progression to bladder augmentation [672, 708]. Beta-3 agonists like mirabegron as an adjuvant treatment has been shown to be effective and safe in some recent studies of children (> 5 years) and adolescents [709-712].

Alpha-adrenergic antagonists may facilitate emptying in children with neurogenic bladder [713]. Doxazosin with an initial dose of 0.5 to 1.0 mg or tamsulosin hydrochloride in a medium (0.0002-0.0004 mg/kg/day) or high dose (0.0004-0,0008 mg/kg/day) has been given to children with neurogenic bladders [713-715]. It was well tolerated but not effective at least in one study [714].

Botulinum toxin A injections: In neurogenic bladders that are refractory to anticholinergics, the off-label use of suburothelial or intramuscular injection of onabotulinum toxin A into the detrusor muscle is a treatment option [653, 654]. In children, continence could be achieved in 32-100% of patients, a decrease in maximum detrusor pressure of 32% to 54%, an increase of maximum cystometric capacity from 27% to 162%, and an improvement in bladder compliance of 28%-176% [653]. Onabotulinum toxin A seems to be more effective in bladders with obvious detrusor muscle over-activity, whereas non-compliant bladders without obvious contractions are unlikely to respond [716, 717]. Also, the injections into the trigone seems to be save in regard of reflux and upper tract damage; if it has some benefit is not further investigated [657]. Of the patients with failed augmentation cystoplasty, 43% responded well to intra-detrusor onabotulinum toxin A injections in a recent series of 30 patients [718].

The most used dose of onabotulinum toxin A is 10 to 12 U/kg with a maximum dose between 200 U and 360 U [719]. A recent randomized trail demonstrated, that 200IE have greater efficacy in reducing bladder pressure

and increasing bladder capacity compared to 50 or 100IE [720]. Onabotolinum toxin A can be effective between three to twelve (0-25) months and repeated injections are effective up to ten years in one study [721-723].

Urethral sphincter onabotulinum toxin A injection has been shown to be effective in decreasing urethral resistance and improve voiding. The evidence is still too low to recommend its routine use in decreasing outlet resistance, but it could be considered as an alternative in refractory cases [724, 725].

Neuromodulation
Intravesical electrical stimulation of the bladder [726-728], sacral nerve stimulation [729, 730] and transcutaneous neuromodulation [668] are still experimental and cannot be recommended outside of clinical trials. The same is true for the intradural somatic-to-autonomic nerve anastomosis [731, 732].

Urethral Dilatation
The aim is to lower the pop-off pressure by lowering the detrusor leak-point pressure by dilatation of the external sphincter under general anaesthesia up to 36 Charr. Some studies showed, that especially in females, the procedure is safe and in selected patients, effective [733-735].

Vesicostomy
Vesicostomy - preferably a Blocksom stoma [736] - is an option to reduce bladder pressure in children/new-borns, if the caregivers are incompliant with IC and/or IC through the urethra is extremely difficult or impossible [737]. Especially in the young infant with severe upper tract dilatation or infections, a vesicostomy should be considered. In some patients it may be also a good long-term solution to prevent infection and renal deterioration [738]. Drawbacks are the difficulty fitting and maintaining a collecting appliance in older patients. A cystostomy button may be an alternative, with a complication rate (mostly UTI) of up to 34% within a mean follow-up of 37 months [739].

3.12.4.3 Management of faecal incontinence

Children with neurogenic bladder usually have also a neurogenic bowel function. Faecal incontinence may have an even greater impact on QoL, as the odour can be a reason for social isolation. The aim of each treatment is to obtain a smooth, regular bowel emptying and to achieve continence and impendence. The regime should be tailored to the patient's need, which may change over time. Beside a diet with small portioned fibre food and adequate fluid intake to keep a good fluid balance [686], follow-up options should be offered to the patients and caregivers.

In the beginning, faecal incontinence is managed most commonly with mild laxatives, such as mineral oil, combined with enemas to facilitate removal of bowel contents. To enable the child to defecate once a day at a given time, rectal suppositories as well as digital stimulation by parents or caregivers can be used. Today, transanal irrigation is one of the most important treatments for patients with neurogenic bowel incontinence. Regular irrigations significantly reduce the risk for faecal incontinence also in the long run in up to 90% of the patients [740]. The risk of irrigation induced perforation of the bowel is estimated as one per 50,000 [678]. During childhood, most children depend on the help of the caregivers. Later in some patients, transanal irrigation becomes difficult or impossible due to anatomic or social circumstances. In these patients antegrade irrigation using a MACE-stoma (Malone Antegrade Continence Enema) is an option, which can also be placed in the left abdomen [741, 742]. In a long-term study of 105 patients with a MACE stoma, 69% had successful bowel management. They were started on normal saline, but some switched to GoLYTELY (PEG-3350 and electrolyte solution). Additives (biscodyl, glycerin etc.) were needed in 34% of patients. Stomal complications occurred in 63% (infection, leakage, and stenosis) of patients, 33% required surgical revision and 6% eventually required diverting ostomies [743]. In addition, patients need to be informed, that the antegrade irrigation is also time consuming taking at least 20-60 minutes.

3.12.4.4 Urinary tract infection

Urinary tract infections are common in children with neurogenic bladders. However, there is no consensus in most European centres, for prevention, diagnosing and treating UTIs in children with neurogenic bladders performing CIC [744]. Although bacteriuria is seen in more than half of children on CIC, patients who are asymptomatic do not need treatment [745, 746]. Continuous antibiotic prophylaxis (CAP) creates more bacterial resistance as demonstrated by a randomized study. Those that stopped the prophylaxis had reduced bacterial resistance, however, 38 out of 88 started antibiotic prophylaxis again due to recurrent UTIs or the caregivers request [747]. A cohort study with 20 patients confirmed these findings. Continuous antibiotic prophylaxis was not protective against the development of symptomatic UTIs and new renal scarring but increased the risk of bacterial resistance [748]. A randomized study in 20 children showed that

cranberry capsules significantly reduced the UTI-rate as well as the rate of bacteriuria [749]. If VUR is present, prophylactic antibiotics should be started when patients experience recurrent UTIs [750, 751].

3.12.4.4.1 Urinary tract infection and clean intermittent catheterisation

The incidence of asymptomatic bacteriuria ranges between 42%-76% [676, 686, 752]. A cross-over study in 40 children with neurogenic bladder demonstrated, that the reuse of CIC-catheters for up to three weeks compared to one week increased the prevalence of bacteriuria from 34% to 74% (it was 60% at the start of the study). During the study-period of eighteen weeks, none of the patients developed a febrile UTI [753]. There is no medical benefit in performing CAP in children with neurogenic bladder, who perform CIC [686]. In those with recurrent UTI, intravesical instillation of gentamycin or neomycin/polymyxin may be an option [754, 755].

Reflux

Secondary reflux in patients with neurogenic bladder increases the risk for pyelonephritis. The treatment is primary related to bladder function including anticholinergic therapy, CIC and may be later augmentation [756]. Those with early and post-therapy persistent reflux during videourodynamic studies at low pressure have a higher risk of pyelonephritis [757]. Patients with a high-grade reflux before augmentation have a higher risk of persistent symptomatic reflux after the enterocystoplasty [758]. Therefore simultaneous ureteral re-implantation in high-grade symptomatic reflux especially in those with low-pressure high-grade reflux should be discussed with the patient/caregivers. Endoscopic treatment has a failure rate of up to 75% after a median follow-up of 4.5 years [759] which is in contrast to the open techniques with a higher success rate but may have an increased risk of inducing obstruction [760].

3.12.4.5 Sexuality

Sexuality, while not an issue in childhood, becomes progressively more important as the patient gets older. This issue has historically been overlooked in individuals with myelodysplasia. However, patients with myelodysplasia do have sexual encounters [761]. The prevalence of precocious puberty is higher in girls with meningomyelocele [762]. Studies indicate that at least 15-20% of males are capable of fathering children and 70% of females can conceive and carry a pregnancy to term. It is therefore important to counsel patients about sexual development in early adolescence.

Women seem to be more sexually active than men in some studies from the Netherlands and the USA [761, 763]. The level of the lesion was the main predictor to be sexually active [764, 765]. Erectile function can be improved by sildenafil in up to 80% of the male patients [766, 767]. Neurosurgical anastomosis between the inguinal nerve and the dorsal penile nerve in patients with a lesion below L3 and disturbed sensation is still to be considered as an experimental treatment [763, 768]. Only 17% to one third of the patients talk to their doctors about sexuality, 25–68% were informed by their doctors about reproductive function [761]. Continence seems to play an important role too. Nine out eleven females without sexual dysfunction reported continence, whereas 50 out of 59 with sexual dysfunction have some urinary incontinence in a recent study [769]. Therefore, early discussion about sexuality in the adolescent is recommended and should be promoted by the paediatric urologist taking care of these patients.

3.12.4.6 Bladder augmentation

In patients where conservative treatment including onabotulinum toxin A (for indication see 3.12.4.3) fails to keep a low-pressure reservoir with a good capacity and compliance, bladder augmentation should be offered. For augmentation, ileal and colonic segments can be used [770]. Gastric segments are rarely used due to its associated complications like the haematuria-dysuria syndrome as well as secondary malignancies, which arise earlier than with other intestinal segments [771-774]. Enterocystoplasty increases bladder capacity, reduces storage pressure and can improve UUT drainage [775]. A good socially acceptable continence rate can be achieved with or without additional bladder outlet procedures [776]. In those, who are not able to perform CIC through the urethra, a continent cutaneous channel should be offered. One recent study in 10 patients showed that thoracic epidural analgesia appears to be a safe and effective opioid sparing option to assist with postoperative pain management following lower urinary tract reconstruction [777]. Surgical complications and revision rate in this group of patients is high. The 30-day all over event rate in the American College of Surgeons' National Surgical Quality Database is approximately 30% (23-33%) with a re-operation rate in this short time period of 13% [778, 779]. In these patients with long-life expectancy the complication rate clearly increases with the follow-up period [780]. The ten-year cumulative complication incidence from the Paediatric Health Information System showed a rate of bladder rupture in up to 6.4%, small bowel obstruction in up to 10.3%, bladder stones in 36%, pyelonephritis in more than a third of the patients and a re-augmentation rate of up to 13% [781]. Bladder perforation, as one of the worst complications, occurs in 3-13% [782]. The rate of VP-shunt infections after gastrointestinal and urological procedures ranges between

0-22%. In a recent study, bowel preparation seems not to have a significant influence on the infection rate (10.5% vs. 8.3%) [783]. Not only surgical complications must be considered; also metabolic complications and consequences after incorporating bowel segments have to be taken into account, such as imbalance of the acid base balance, decrease in vitamin B12 levels and loss of bone density. Stool frequency can increase as well as diarrhoea after exclusion of bowel segments [784] and last, but not least, these patients have a lifelong increased risk to develop secondary malignancies [785, 786]. Therefore, a lifelong follow-up of these patients is required including physical examination, US, blood gas analysis, (pH and base excess), renal function and vitamin B12 if Ileum is used. Endoscopic evaluation starting ten years after augmentation is not cost-effective [787, 788], but may prevent some advanced cancer. Woodhouse *et al*. do not recommend cystoscopy within the first fifteen years after surgery [789]. The real value of annual cystoscopic evaluation has not been proven by any study. Urodynamic studies after bladder augmentation are only indicated, if upper tract dilatation and/or incontinence after the operation has not improved [790].

Adverse effects of intestinal cystoplasties can be avoided by the use of ureterocystoplasty. The combination of a small contracted bladder, associated with a severe dilation of the ureter of a non-functioning kidney is quite rare. The technique was first described in 1973 by Eckstein [791]; the success rate depends on patient selection and the re-augmentation rate can reach 73% [792, 793].

Auto-augmentation with partial detrusorectomy or detrusormyotomy creating a diverticulum avoids metabolic complications with the use of intestinal segments. The reports are conflicting, therefore, it may be used in selected cases [794-797]. For a successful outcome, a pre-operative bladder capacity of 75-80% of the expected volume seems necessary [795, 798]. Seromuscular cystoplasty has also not proven to be as successful as standard augmentation with intestine [799]. Tissue engineering, even if successful in vitro and some animal models, does not reach the results by using intestinal segments with a higher complication rate [800, 801]. Therefore, these alternatives for bladder augmentation should be considered as experimental and should be used only in controlled trials.

3.12.4.7 Bladder outlet procedures

No available medical treatment has been validated to increase bladder outlet resistance. Alpha-adrenergic receptor stimulation of the bladder neck has not been effective [713]. Using fascial slings with autologous fascial strip or artificial material a continence rate between 40-100% can be achieved. In most cases this is achieved in combination with bladder augmentation [802-807]. Catheterising through a reconstructed bladder neck or a urethra compressed by a sling may not be easy; many surgeons prefer to combine this approach with a catheterisable channel [659]. In contrast to the autologous slings, artificial slings in girls with CIC through the urethra have a high complication rate [808]. In males, it may be an option [809], however as long as long-term results are missing, this method has to be classified as experimental and should only be carried out in studies. Artificial urinary sphincters were introduced by Scott in 1973 [810]. The continence rates in the literature in selected patients can be up to 83% [811, 812]. Post-pubertal patients, who can void voluntary are good candidates, if they are manually dexterous. In very selected patients, CIC through the sphincter in an augmented bladder is possible [812]. The erosion rate can be up to 29% and the revision rate up to 100% depending on the follow-up time [806].

Patients, who underwent a bladder neck procedure only, have a chance of > 30% for an augmentation and/or onabotulinum toxin A injections > 30% later on; half of them developed new upper tract damage in that time [813-815]. In patients with a good bladder capacity and bladder compliance without an indication for bladder augmentation, up to 40% will need augmentation later on [814]. Therefore, close follow-up of these patients with UD is required to avoid upper tract damage and chronic renal failure.

Bladder neck reconstruction is used mostly in exstrophy patients with acceptable results. However, in children with a neurogenic bladder the results are less favourable [816]. In most patients, the creation of a continent catheterisable stoma is necessary due to difficulties in performing the CIC via the urethra. In one series, 10% to a third still performed CIC via the urethra with a re-operation rates between 67% and 79% after a median follow-up between seven and ten years [817]. In patients who are still incontinent after a bladder outlet procedure, bladder neck closure with a continent catheterisable stoma is an option. The combination of a sling procedure together with a urethral lengthening procedure may improve the continence rates [818].

Bulking agents have a low success rate (10-40%), which is in most cases only temporary [819-821]. However, it does not adversely affect the outcome of further definite surgical procedures [819].

Bladder neck closure is often seen as the last resort to gain urinary continence in those patients with persistent urinary incontinence through the urethra. In girls, the transection is done between bladder neck and urethra and in boys above the prostate with preservation of the neurovascular bundle. It is an effective method to achieve continence together with a catheterisable cutaneous channel +/- augmentation as a primary or secondary procedure [822, 823]. A complication rate of up to a third and a vesicourethral/vesicovaginal fistula in up to 15% should be considered [824], together with a higher risk for bladder stones, bladder perforation and deterioration of the upper tract function, if the patient is not compliant with CIC and bladder irrigations [824, 825].

3.12.4.8 Catheterisable cutaneous channel.
In most patients with a neurogenic bladder CIC is required. If this is not possible, or very time and/or resource consuming via the urethra, a continent cutaneous catheterisable channel should be offered as well as in those with bladder outlet procedures. It is especially beneficial to wheelchair-bound patients who often have difficulty with urethral catheterisation or are dependent on others to catheterise the bladder. In long-term studies the revision rate due to stenosis or incontinence can be as high as 50-60% depending on the type of channel [826, 827].

The stoma can be placed at the umbilicus or in the lower right abdominal wall using a VQZ plasty [828]. It should be carefully evaluated pre-operatively: it is extremely important that the patient can reach the stoma easily. Sometimes it has to be placed in the upper abdominal wall due to sever scoliosis mostly associated with obesity.

3.12.4.9 Continent and incontinent cutaneous urinary diversion
Incontinent urinary diversion should be considered in patients who are not willing or able to perform a CIC and who need urinary diversion because of upper tract deterioration or gain urinary continence due to social reasons. In children and adolescents, the colonic conduit has shown to have less complications compared to the ileal conduit [829-832]. Total bladder replacement is extremely rare in children and adolescents, but may be necessary in some adults due to secondary malignancies or complications with urinary diversions. Any type of major bladder and bladder outlet construction should be performed in centres with sufficient experience in the surgical technique, and with experienced healthcare personnel to carry out post-operative follow-up [776, 833, 834].

Algorithms can be used for management of these patients (Figures 7 and 8).

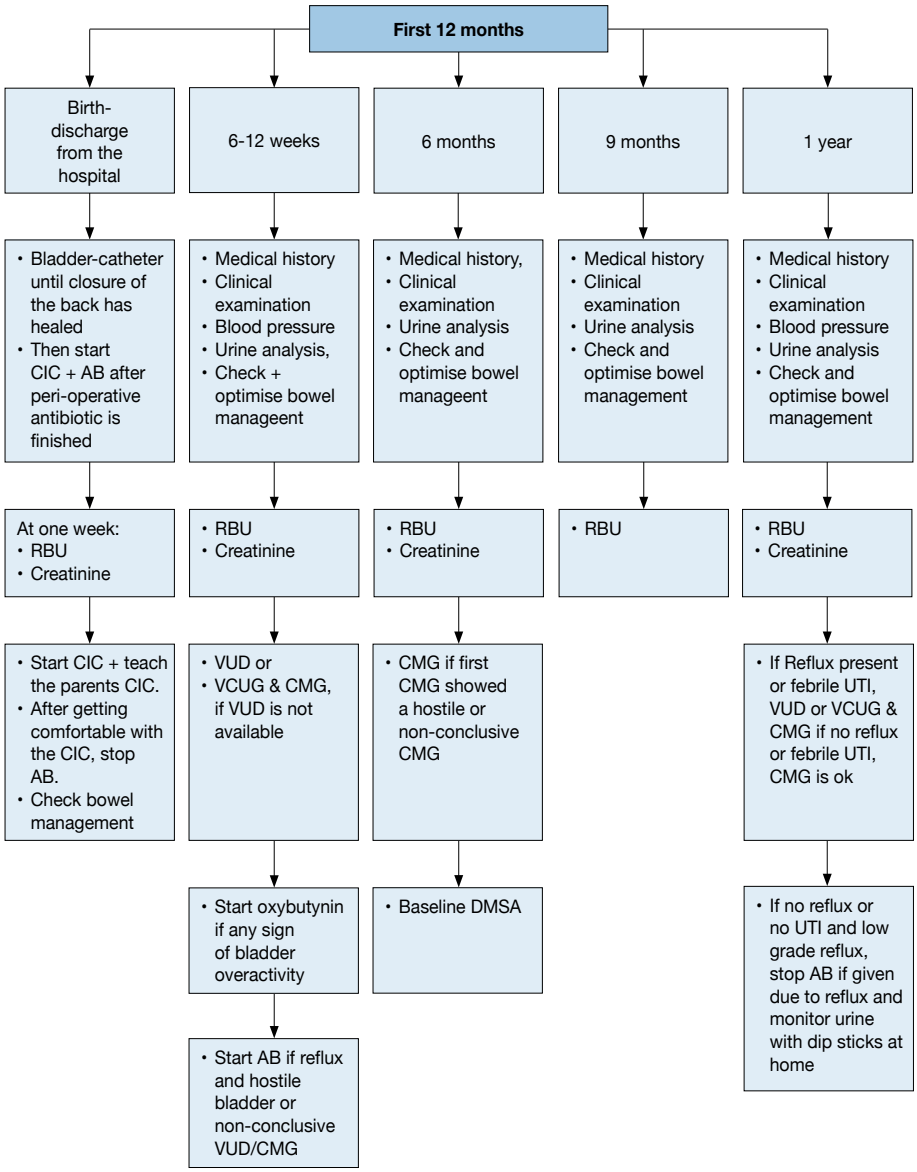
*3.12.5 **Follow-up***
Neurogenic bladder patients require lifelong follow-up including not only urological aspects but also neurological and orthopaedic aspects. Regular investigation of upper and lower urinary tract is mandatory. In patients with changes of the function of the upper and/or lower urinary tract, a complete neurological re-investigation should be recommended including a total spine MRI to exclude a secondary tethered cord or worsening of the hydrocephalus. In addition, if some neurological changes are observed a complete investigation of the urinary tract should be undertaken.

A recent study of this guideline panel revealed that the priorities of patients for future expectations were as following in decreasing order: QoL, surgical techniques, development of new medications and sexuality/ fertility issues. Male spina bifida patients preferred new medications and sex/fertility issues more, whereas females favoured QoL issues improvement more. These factors should be considered during long-term management [2].

In those patients with urinary tract reconstruction using bowel segments, regular investigations concerning renal function, acid base balance and vitamin B12 status are mandatory to avoid metabolic complications. There is an increased risk for secondary malignancies in patients with a neurogenic bladder either with or without enteric bladder augmentations [835-839]. Therefore, patients need to be informed of this risk and possible signs like haematuria. Although there are insufficient data on follow-up schemes to discover secondary malignancies, after a reasonable follow-up time (e.g. ten to fifteen years), an annual cystoscopy can be considered.

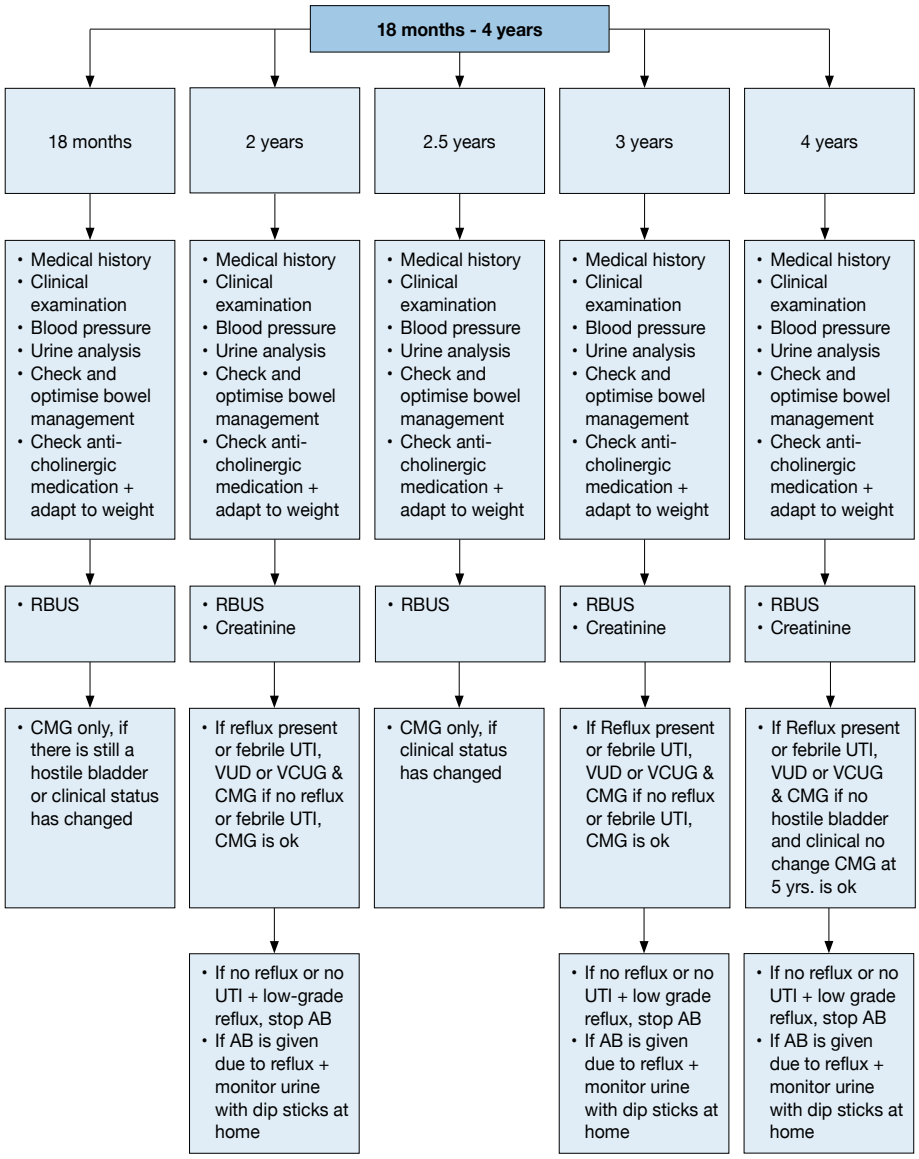
*3.12.6 **Self-organisation of patients***
As patients' self-organisations can support the parents, caregivers and the patients in all aspects of their daily life, patients should be encouraged to join these organisations.

Figure 7a: Management of children with myelodysplasia with a neurogenic bladder
Flowchart - First year of life


First 12 months
Birth-discharge from the hospital
6-12 weeks
6 months
9 months
1 year
• Bladder-catheter until closure of the back has healed
• Then start CIC + AB after peri-operative antibiotic is finished
• Medical history
• Clinical examination
• Blood pressure
• Urine analysis,
• Check + optimise bowel manageent
• Medical history,
• Clinical examination
• Urine analysis
• Check and optimise bowel manageent
• Medical history
• Clinical examination
• Urine analysis
• Check and optimise bowel management
• Medical history
• Clinical examination
• Blood pressure
• Urine analysis
• Check and optimise bowel management
At one week:
• RBU
• Creatinine
• RBU
• Creatinine
• RBU
• Creatinine
• RBU
• RBU
• Creatinine
• Start CIC + teach the parents CIC.
• After getting comfortable with the CIC, stop AB.
• Check bowel management
• VUD or
• VCUG & CMG, if VUD is not available
• CMG if first CMG showed a hostile or non-conclusive CMG
• If Reflux present or febrile UTI, VUD or VCUG & CMG if no reflux or febrile UTI, CMG is ok
• Start oxybutynin if any sign of bladder overactivity
• Baseline DMSA
• If no reflux or no UTI and low grade reflux, stop AB if given due to reflux and monitor urine with dip sticks at home
• Start AB if reflux and hostile bladder or non-conclusive VUD/CMG

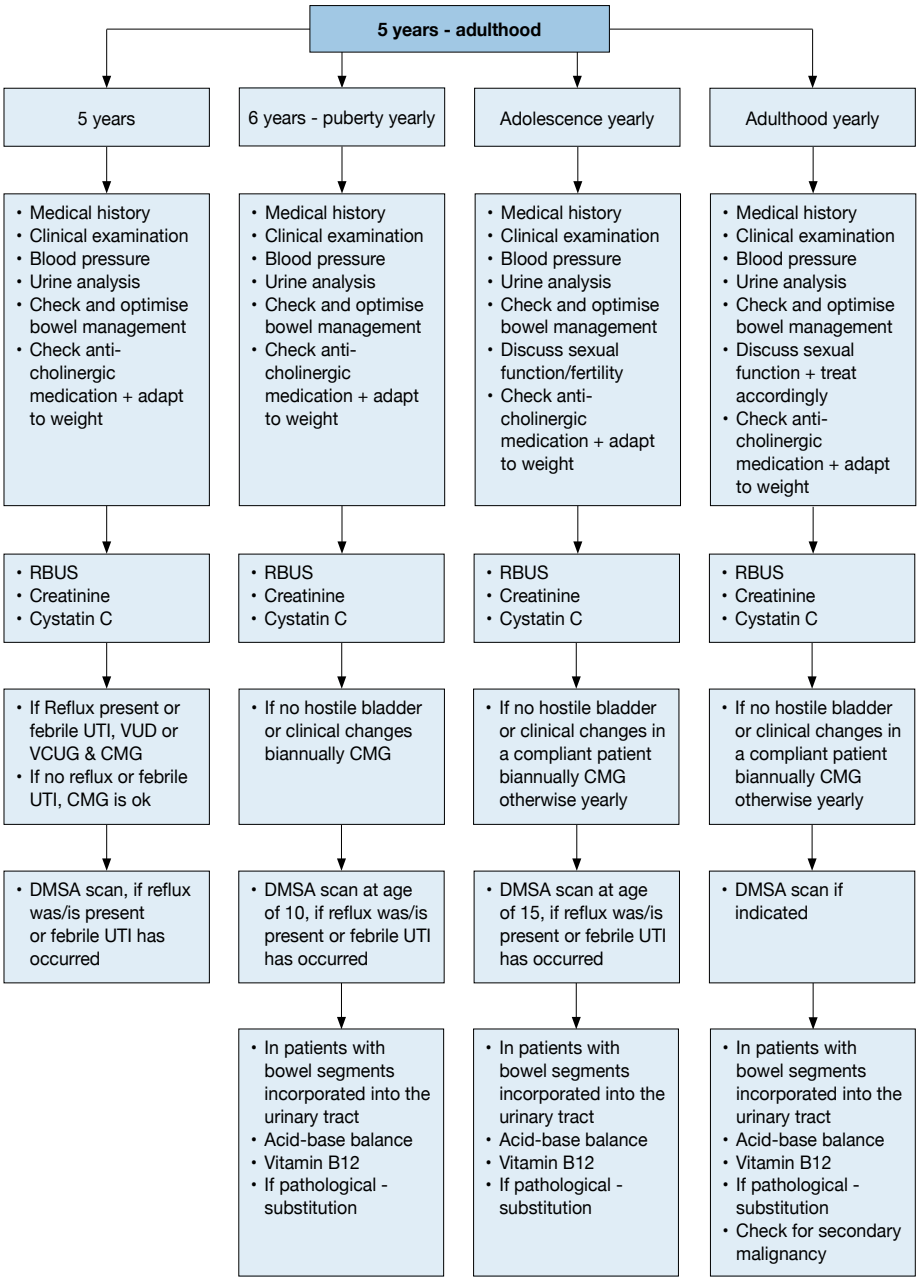
RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid; AB = antibiotics.

Figure 7b: Management of children with myelodysplasia with a neurogenic bladder
Flowchart - 18 months - 4 years of age


18 months - 4 years
18 months
2 years
2.5 years
3 years
4 years
• Medical history
• Clinical examination
• Blood pressure
• Urine analysis
• Check and optimise bowel management
• Check anti-cholinergic medication + adapt to weight
• RBUS
• RBUS
• Creatinine
• CMG only, if there is still a hostile bladder or clinical status has changed
• If reflux present or febrile UTI, VUD or VCUG & CMG if no reflux or febrile UTI, CMG is ok
• CMG only, if clinical status has changed
• If Reflux present or febrile UTI, VUD or VCUG & CMG if no reflux or febrile UTI, CMG is ok
• If Reflux present or febrile UTI, VUD or VCUG & CMG if no hostile bladder and clinical no change CMG at 5 yrs. is ok
• If no reflux or no UTI + low-grade reflux, stop AB
• If AB is given due to reflux + monitor urine with dip sticks at home
• If no reflux or no UTI + low grade reflux, stop AB
• If AB is given due to reflux + monitor urine with dip sticks at home

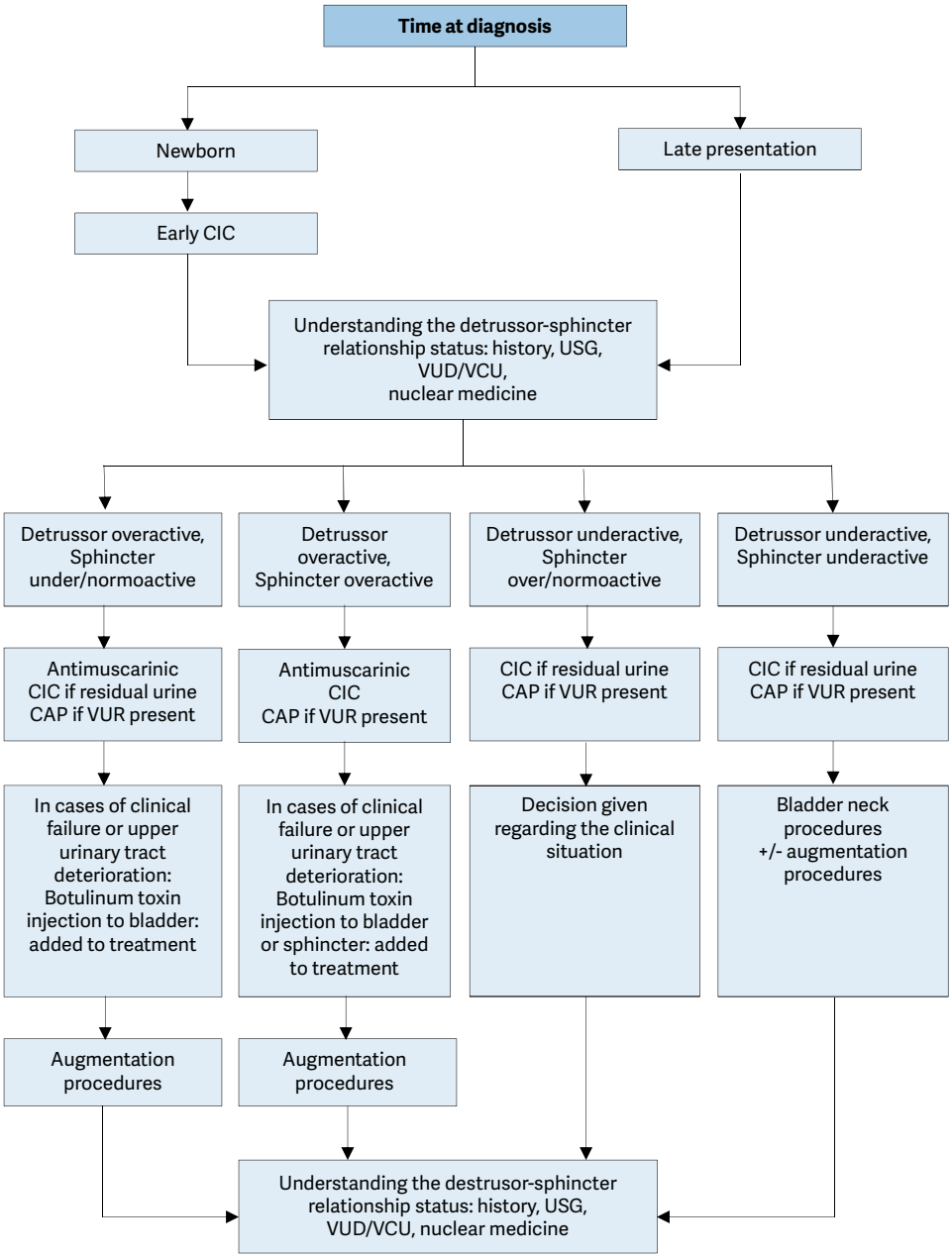
RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid; AB = antibiotics

Figure 7c: Management of children with myelodysplasia with a neurogenic bladder
Flowchart - 5 years to adulthood


5 years - adulthood
5 years
6 years - puberty yearly
Adolescence yearly
Adulthood yearly
• Medical history
• Clinical examination
• Blood pressure
• Urine analysis
• Check and optimise bowel management
• Check anti-cholinergic medication + adapt to weight
• Discuss sexual function/fertility
• Discuss sexual function + treat accordingly
• RBUS
• Creatinine
• Cystatin C
• If Reflux present or febrile UTI, VUD or VCUG & CMG
• If no reflux or febrile UTI, CMG is ok
• If no hostile bladder or clinical changes biannually CMG
• If no hostile bladder or clinical changes in a compliant patient biannually CMG otherwise yearly
• DMSA scan, if reflux was/is present or febrile UTI has occurred
• DMSA scan at age of 10, if reflux was/is present or febrile UTI has occurred
• DMSA scan at age of 15, if reflux was/is present or febrile UTI has occurred
• DMSA scan if indicated
• In patients with bowel segments incorporated into the urinary tract
• Acid-base balance
• Vitamin B12
• If pathological - substitution
• Check for secondary malignancy

RBUS = Renal bladder ultrasound; UTI = urinary tract infection; VUD = videourodynamic; VCUG = voiding cystourethrography; CMG = cystometrogram; DMSA = dimercaptosuccinic acid.

Figure 8: Algorithm for the management of children with myelodysplasia with a neurogenic bladder


Time at diagnosis
Newborn
Late presentation
Early CIC
Understanding the detrussor-sphincter relationship status: history, USG, VUD/VCU, nuclear medicine
Detrussor overactive, Sphincter under/normoactive
Detrussor overactive, Sphincter overactive
Detrussor underactive, Sphincter over/normoactive
Detrussor underactive, Sphincter underactive
Antimuscarinic CIC if residual urine CAP if VUR present
Antimuscarinic CIC CAP if VUR present
CIC if residual urine CAP if VUR present
CIC if residual urine CAP if VUR present
In cases of clinical failure or upper urinary tract deterioration: Botulinum toxin injection to bladder: added to treatment
In cases of clinical failure or upper urinary tract deterioration: Botulinum toxin injection to bladder or sphincter: added to treatment
Decision given regarding the clinical situation
Bladder neck procedures +/- augmentation procedures
Augmentation procedures
Augmentation procedures
Understanding the destrusor-sphincter relationship status: history, USG, VUD/VCU, nuclear medicine

CAP = continuous antibiotic prophylaxis; CIC = clean intermittent catheterisation; US = ultrasound; VCUG = voiding cystourethrography; VUD = videourodynamic; VUR = vesicoureteric reflux.

3.12.7 *Summary of evidence and recommendations for the management of neurogenic bladder*

Summary of evidence	LE
Neurogenic detrusor-sphincter dysfunction (NDSD) may result in different forms of LUTD and ultimately result in incontinence, UTIs, VUR, and renal scarring.	2a
In children, the most common cause of NDSD is myelodysplasia (a group of developmental anomalies that result from defects in neural tube closure).	2
Bladder sphincter dysfunction correlates poorly with the type and level of the spinal cord lesion. Therefore, urodynamic and functional classifications are more practical in defining the extent of the pathology and in guiding treatment planning.	2a
Children with neurogenic bladder can have disturbances of bowel function as well as urinary function which require monitoring and, if needed, management.	2a
The main goals of treatment are prevention of urinary tract deterioration and achievement of continence at an appropriate age.	2a
Injection of botulinum toxin into the detrusor muscle in children who are refractory to anticholinergics, has been shown to have beneficial effects on clinical and urodynamic variables.	2a

Recommendations	LE	Strength rating
Urodynamic studies should be performed in every patient with spina bifida as well as in every child with high suspicion of a neurogenic bladder to estimate the risk for the upper urinary tract and to evaluate the function of the detrusor and the sphincter.	2	Strong
In all newborns, intermittent catheterisation (IC) should be started soon after birth. In those with a clear underactive sphincter and no overactivity, starting IC may be delayed. If IC is delayed, closely monitor babies for urinary tract infections, upper tract changes (US) and the lower tract (UD).	3	Strong
Start early anticholinergic medication in the newborns with suspicion of an overactive detrusor.	2	Strong
The use of suburothelial or intradetrusoral injection of onabotulinum toxin A is an alternative and a less invasive option in children who are refractory to anticholinergics in contrast to bladder augmentation.	2	Strong
Treatment of faecal incontinence is important to gain continence and independence. Treatment should be started with mild laxatives, rectal suppositories as well as digital stimulation. If not sufficient transanal irrigation is recommended, if not practicable or feasible, a Malone antegrade colonic enema (MACE)/Antegrade continence enema (ACE) stoma should be discussed.	3	Strong
Ileal or colonic bladder augmentation is recommended in patients with therapy resistant overactivity of the detrusor, small capacity and poor compliance, which may cause upper tract damage and incontinence. The risk of surgical and non-surgical complications and consequences outweigh the risk of permanent damage of the upper urinary tract +/- incontinence due to the detrusor.	2	Strong
In patients with a neurogenic bladder and a weak sphincter, a bladder outlet procedure should be offered. It should be done in most patients together with a bladder augmentation.	3	Weak
Creation of a continent cutaneous catheterisable channel should be offered to patients who have difficulties in performing an IC through the urethra.	3	Weak
A life-long follow-up of renal and reservoir function should be available and offered to every patient. Addressing sexuality and fertility starting before/during puberty should be offered.	3	Weak
Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated.	3	Weak

3.13 Dilatation of the upper urinary tract (UPJ and UVJ obstruction)

*3.13.1 **Epidemiology, aetiology and pathophysiology***

Dilatation of the upper urinary tract (UUT) remains a significant clinical challenge in deciding which patient will benefit from treatment. Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter with subsequent dilatation of the collecting system and the potential to damage the kidney. It is the most common pathological cause of neonatal hydronephrosis [840]. It has an overall incidence of 1:1,500 and a ratio of males to females of 2:1 in newborns.

Ureterovesical junction (UVJ) obstruction is an obstructive condition of the distal ureter as it enters the bladder, commonly called a primary obstructive megaureter. Megaureters are the second most likely cause of pathological neonatal hydronephrosis. They occur more often in males and are more likely to occur on the left side [841]. It can be very difficult to define 'obstruction' as there is no clear division between 'obstructed' and 'non-obstructed' urinary tracts. Currently, the most popular definition is that an obstruction represents any restriction to urinary outflow that, if left untreated, will cause progressive renal deterioration [842].

*3.13.2 **Diagnostic evaluation***

The widespread use of US during pregnancy has resulted in a higher detection rate for antenatal hydronephrosis [843]. The challenge in the management of dilated UUT is to decide which child should be observed, which should be managed medically, and which requires surgical intervention. Despite the wide range of diagnostic tests, there is no single test that can accurately distinguish obstructive from non-obstructive cases (see Figure 9).

3.13.2.1 Antenatal ultrasound

Usually between the 16th and 18th weeks of pregnancy, the kidneys are visualised routinely, when almost all amniotic fluid consists of urine. The most sensitive time for foetal urinary tract evaluation is the 28th week. If dilatation is detected, US should focus on:

- laterality, severity of dilatation, and echogenicity of the kidneys;
- hydronephrosis or hydro-ureteronephrosis;
- bladder volume and bladder emptying;
- sex of the child;
- amniotic fluid volume [844].

3.13.2.2 Postnatal ultrasound

Since transitory neonatal dehydration lasts about 48 hours after birth, imaging should be performed following this period of postnatal oliguria. However, in severe cases (bilateral dilatation, solitary kidney, oligohydramnios), immediate postnatal sonography is recommended [845]. Ultrasound should assess the anteroposterior diameter of the renal pelvis, calyceal dilatation, kidney size, thickness of the parenchyma, cortical echogenicity, ureters, bladder wall and residual urine.

3.13.2.3 Voiding cystourethrogram

In newborns with identified UUT dilatation, the primary or important associated factors that must be detected include:

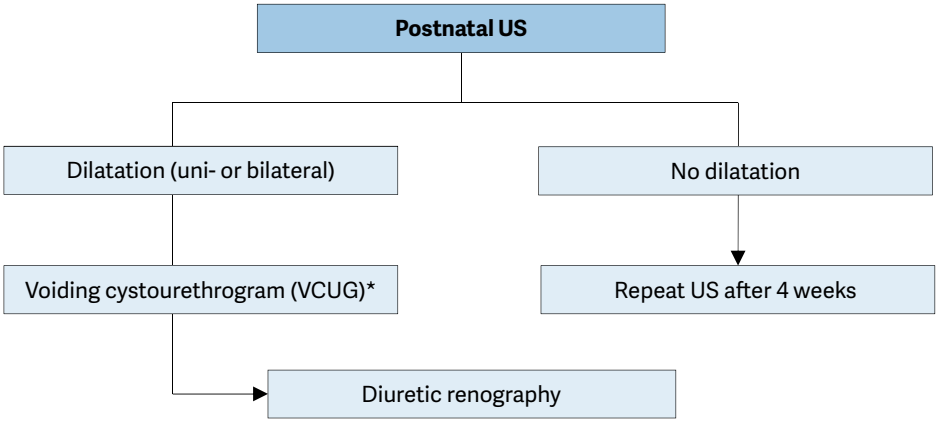
- vesicoureteral reflux (found in up to 25% of affected children) [846];
- urethral valves;
- ureteroceles;
- diverticula;
- neurogenic bladder.

Conventional VCUG is the method of choice for primary diagnostic procedures [847].

3.13.2.4 Diuretic renography

Diuretic renography is the most commonly used diagnostic tool to detect the severity and functional significance of problems with urine transport. Technetium-99m (^{99m}Tc) mercaptoacetyltriglycine (MAG3) is the radionuclide of choice. It is important to perform the study under standardised circumstances (hydration, transurethral catheter) after the fourth and sixth weeks of life [848]. Oral fluid intake is encouraged prior to the examination. At fifteen minutes before the injection of the radionuclide, it is mandatory to administer normal saline intravenous infusion at a rate of 15 mL/kg over 30 minutes, with a subsequent maintenance rate of 4 mL/kg/h throughout the entire time of the investigation [849]. The recommended dose of furosemide is 1 mg/kg for infants during the first year of life, while 0.5 mg/kg should be given to children aged one to sixteen years, up to a maximum dose of 40 mg.

Figure 9: Diagnostic algorithm for dilatation of the upper urinary tract



** A diagnostic work-up including VCUG must be discussed with the caregivers, as it is possible that, even if reflux is detected, it may have absolutely no clinical impact. However, it should be borne in mind that reflux has been detected in up to 25% of cases of prenatally detected and postnatally confirmed hydronephrosis [757].*
US = ultrasound.

*3.13.3 **Management***

3.13.3.1 Prenatal management

Counselling the caregivers of an affected child is one of the most important aspects of care. The prognosis is hopeful for a hydronephrotic kidney, even if it is severely affected, as it may still be capable of meaningful renal function, unlike a severely hypoplastic and dysplastic kidney.

It is important to be able to tell the caregivers exactly when they will have a definitive diagnosis for their child and what this diagnosis will mean. In some cases, however, it will be immediately obvious that the child is severely affected; there will be evidence of massive bilateral dilatation, bilateral hypoplastic dysplasia, progressive bilateral dilatation with oligohydramnios, and pulmonary hypoplasia.

Intrauterine intervention is rarely indicated and should only be performed in well-experienced centres [850].

3.13.3.1.1 Antibiotic prophylaxis for antenatal hydronephrosis

The benefits and harms of continous antibiotic prophylaxis (CAP) vs. observation in patients with antenatal hydronephrosis are controversial. Currently, only two RCTs have been published, one of which is a pilot trial [851] and the other publication is only available as a congress abstract [852]. Both publications present incomplete data and outcomes.

The Panel conducted a SR assessing the literature from 1980 onwards [853]. The key findings are summarised below.

Due to the heterogeneity of the published literature it was not possible to draw strong conclusions as to whether CAP is superior to observation alone in children diagnosed with antibiotic prophylaxis for antenatal hydronephrosis (ANH). In the first RCT, a prospective longitudinal study [851], female gender, uncircumcised males, lack of CAP, high-grade hydronephrosis, hydroureteronephrosis and VUR were found to be the independent predictors for the development of UTI. The second RCT included in the SR, was published as an abstract only, presented limited data [852]. This trial seemed to focus mainly on patients with ANH and VUR and did not report any beneficial effect of CAP on UTI rates, but details on the study population were limited.

Key findings of the SR are that CAP may or may not be superior to observation in children with antenatal hydronephrosis in terms of decreasing UTI. Due to the low data quality it was also not possible to establish whether boys or girls are at a greater risk of developing a UTI, or ascertain whether the presence or absence of VUR impacts UTI rates. A correlation between VUR-grade and UTI could not be established either. However, noncircumcised infants, children diagnosed with high-grade hydronephrosis and hydroureteronephrosis were shown to be at higher risk of developing a UTI.

The SR also tried to identify the most effective antibiotic regimen and present data on adverse effects but, due to heterogeneity, the available data could not be statistically compared. The most commonly used antibiotic in infants with antenatal hydronephrosis is trimethoprim, but only one study reported side effects [851].

In conclusion, based on the available evidence, the benefits and harms of CAP in children with antenatal hydronephrosis remain unproven. Uncircumcised infants and infants with hydroureteronephrosis and highgrade hydronephrosis are more likely to develop a UTI. Continuous antibiotic prophylaxis should be reserved for this sub-group of children who are proven to be at high risk.

3.13.3.2 UPJ obstruction

It is most important that management decisions are made on the basis of serial investigations that have used the same technique and have been performed by the same institution under standardised circumstances. According to a Cochrane review, non-surgical management of unilateral UPJ obstruction in infants less than two years old is also an option. However the high risk of bias of the included studies limits the evidence of this systematic review [854].

Symptomatic obstruction (recurrent flank pain, UTI) requires surgical correction using a pyeloplasty, according to the standardised open technique of Hynes and Anderson [855]. In experienced hands, laparoscopic or retroperitoneoscopic techniques and robot-assisted techniques have the same success rates as standard open procedures. In asymptomatic cases, conservative follow-up is the treatment of choice. A recent interventional study suggested that, in operated infants less than six months, inserting a stent (transanastomotic stent) decreases the complication rates compared to stentless approach [856]. However the results should be taken cautiously since there are successful reported stentless procedures in other age groups.

Indications for surgical intervention comprise impaired split renal function (< 40%), a decrease of split renal function of > 10% in subsequent studies, poor drainage function after the administration of furosemide, increased anteroposterior diameter on US, and grade III and IV dilatation as defined by the Society for Fetal Urology [644].

Well-established benefits of conventional laparoscopy over open surgery are the decreased length of hospital stay, better cosmesis, less post-operative pain and early recovery [857, 858]. A recent meta-analysis in children has shown that laparoscopic pyeloplasty (LP) was associated with decreased length of hospital stay and complication rates but prolonged operative time when compared to open pyeloplasty (OP). Additionally, both LP and OP had equal success rates [859]. Laparoscopic pyeloplasty can also be performed for re-do cases with the same advantages of the primary cases [860]. Robotic-assisted laparoscopic pyeloplasty (RALP) has all the same advantages as LP plus better manoeuvrability, improved vision, ease in suturing and increased ergonomics but higher costs [861, 862]. A recent study comparing RALP and LP has shown similar postoperative outcomes with exception of decreased operative time for RALP [863]. There does not seem to be any clear benefit of minimal invasive procedures in a very young child but current data is insufficient to defer a cut-off age.

3.13.3.3 Megaureter

The treatment options of secondary megaureters are reviewed in Chapter 3.14.3.

3.13.3.3.1 Non-operative management

If a functional study reveals and confirms adequate ureteral drainage, conservative management is the best option. Initially, low-dose prophylactic antibiotics within the first year of life are recommended for the prevention of UTIs, although there are no existing prospective randomised trials evaluating the benefit of this regimen [864]. With spontaneous remission rates of up to 85% in primary megaureter cases, surgical management is no longer recommended, except for megaureters with recurrent UTIs, deterioration of split renal function and significant obstruction [865].

3.13.3.3.2 Surgical management

In general, surgery is indicated for symptomatic children, if there is a drop in function in conservative follow-up and hydroureteronephrosis is increasing [866]. Data suggest that children with a ureteric diameter of > 10-15 mm are more likely to require intervention [867].

The initial approach to the ureter can be either intravesical, extravesical or combined. Straightening the ureter is necessary without devascularisation. Ureteral tapering should enhance urinary flow into the bladder. The ureter must be tapered to achieve a diameter for an anti-reflux repair. Several tailoring techniques exist, such as ureteral imbrication or excisional tapering [868]. Some institutions perform endoscopic stenting, but there are still no long-term data and no prospective randomised trials to confirm their outcome. A systematic review assessed the success rates of endoscopic management of primary obstructive megaureters [869]. It was reported that endoscopic managements including; stent placement, balloon dilatation and incision can be an alternative treatment in patients > 1 years of age. One third of those patients required further surgical correction. Furthermore, the long-term outcome of endoscopic management is still unknown. Therefore the EAU Paediatric Urology Guidelines Panel can not recommend endoscopic management routinely since the type of intervention and the management outcomes are unclear.

3.13.4 ***Conclusion***

The use of routine perinatal sonography has resulted in increased detection of hydronephrosis caused by UPJ or UVJ obstruction. Meticulous and repeat postnatal evaluation is mandatory to try to identify obstructive cases at risk of renal deterioration and requiring surgical reconstruction. Surgical methods are standardised and have a good clinical outcome.

3.13.5 ***Summary of evidence and recommendations for the management of UPJ-, UVJ-obstruction***

Summary of evidence	LE
Nowadays, most hydronephrotic kidneys have already been diagnosed prenatally during a maternal US investigation.	2
Ureteropelvic junction obstruction is the leading pathological cause of hydronephrotic kidneys (40%).	1
In children diagnosed with antenatal hydronephrosis, a systematic review could not establish any benefits or harms related to continuous antibiotic prophylaxis.	1b
In children diagnosed with antenatal hydronephrosis, non-circumcised infants (LE: 1a), children diagnosed with high-grade hydronephrosis (LE: 2) and hydroureteronephrosis (LE: 1b) were shown to be at higher risk of developing UTI.	2

Recommendations	LE	Strength rating
Include serial ultrasound (US) and subsequent diuretic renogram and sometimes voiding cystourehrography in postnatal investigations.	2	Strong
Offer continuous antibiotic prophylaxis to the subgroup of children with antenatal hydronephrosis who are at high risk of developing urinary tract infection like uncircumcised infants, children diagnosed with hydroureteronephrosis and high-grade hydronephrosis, respectively.	2	Weak
Decide on surgical intervention based on the time course of the hydronephrosis and the impairment of renal function.	2	Weak
Offer surgical intervention in case of an impaired split renal function due to obstruction or a decrease of split renal function in subsequent studies and increased anteroposterior diameter on the US, and grade IV dilatation as defined by the Society for Fetal Urology.	2	Weak
Offer pyeloplasty when ureteropelvic junction obstruction has been confirmed clinically or with serial imaging studies proving a substantially impaired or decrease in function.	2	Weak
Do not offer surgery as a standard for primary megaureters since the spontaneous remission rates are as high as 85%.	2	Strong

3.14 Vesicoureteric reflux

Lack of robust prospective RCTs limits the strength of the established guidelines for the management of VUR. The scientific literature for reflux disease is still limited and the level of evidence is generally low. Most of the studies are retrospective, include different patient groups, and have poor stratification of quality. Also, there is a high risk of presenting misleading results by combining different types of studies when systematically extracting data. Therefore, for reflux disease, it is unfortunately not possible to produce recommendations based on high-quality studies. The Panel have assessed the current literature, but in the absence of conclusive findings, have provided recommendations based on Panel consensus.

These Guidelines aim to provide a practical approach to the treatment of VUR based on risk analysis and selective indications for both diagnostics and intervention. Although the Panel have tried to summarise most of the possible scenarios in one single table, the table itself is still quite busy. The Panel strongly share the view that making simple and practical guidelines would underestimate the complexity of VUR as a sign of a wide range of pathologies [870].

3.14.1 ***Epidemiology, aetiology and pathophysiology***

Vesicoureteric reflux is an anatomical and/or functional disorder with potentially serious consequences, such as renal scarring, hypertension and renal failure. Patients with VUR present with a wide range of severity, and a good proportion of reflux patients do not develop renal scars and probably do not need any intervention [871]. Vesicoureteric reflux is a very common urological anomaly in children, with an incidence of nearly 1%.

The main management goal is the preservation of kidney function, by minimising the risk of pyelonephritis. By defining and analysing the risk factors for each patient (i.e. age, sex, reflux grade, LUTD, anatomical abnormalities, and kidney status), it is possible to identify those patients with a potential risk of UTIs and renal scarring. Controversy persists over the optimal management of VUR, particularly the choice of diagnostic procedures, treatment (medical, endoscopic or surgical), and the timing of treatment.

Many children present without symptoms of UTI and, because invasive diagnostic procedures are performed only when clinically indicated, the exact prevalence of VUR is unknown. However, the prevalence of VUR in non-symptomatic children has been estimated at 0.4-1.8% [872]. Among infants prenatally identified with hydronephrosis on US, who were screened for VUR, the prevalence was 16.2% (7-35%) [873]. Siblings of children with VUR had a 27.4% (3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a higher incidence of 35.7% (21.2-61.4%) [873].

However, reflux detected by sibling screening is associated with lower grades [781] and significantly earlier resolution [874]. When VUR is discovered in siblings after UTI, it is usually high-grade and associated with a high incidence of reflux nephropathy, particularly if the sibling is male and the grade of reflux was high in the index patient [875].

The incidence of VUR is much higher among children with UTIs (30-50%, depending on age). Urinary tract infections are more common in girls than boys due to anatomical differences. However, among all children with UTIs, boys are more likely to have VUR than girls (29% vs. 14%). Boys also tend to have higher grades of VUR diagnosed at younger ages, although their VUR is more likely to resolve itself [876-879].

There is a clear co-prevalence between LUTD and VUR [880]. Lower urinary tract dysfunction refers to the presence of LUTS, including urge, urge incontinence, weak stream, hesitancy, frequency and UTIs, which reflect the filling and/or emptying dysfunction and may be accompanied with bowel problems [880]. Some studies have described a prevalence of 40-60% for VUR in children with LUTD [881]. A published Swedish reflux trial has demonstrated LUTD in 34% of patients, and subdivision into groups characteristic of children revealed that 9% had isolated overactive bladder and 24% had voiding phase dysfunction [882].

The spontaneous resolution of VUR is dependent on age at presentation, sex, grade, laterality, mode of clinical presentation, and anatomy [874]. Faster resolution of VUR is more likely with age less than one year at presentation, lower grade of reflux (grade 1-3), and asymptomatic presentation with prenatal hydronephrosis or sibling reflux. The overall resolution rate is high in congenital high-grade VUR during the first years of life. In several Scandinavian studies, the complete resolution rate for high-grade VUR has been reported at > 25%, which is higher than the resolution rate for VUR detected after infancy [882-884].

The presence of renal cortical abnormality, bladder dysfunction, and breakthrough febrile UTIs are negative predictive factors for reflux resolution [885-887].

Dilating VUR increases the risk of developing acute pyelonephritis and renal scarring. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. Evidence of renal scarring is present in 10-40% of children with symptomatic VUR, resulting from either congenital dysplasia and/or acquired post-infectious damage, which may have a negative impact on somatic growth and general well-being [888-890].

Scar rates vary in different patient groups. Patients with higher grades of VUR present with higher rates of renal scars. In those with prenatal hydronephrosis, renal scarring occurs in 10% of patients [891-896], whereas in patients with LUTD, this may increase up to 30% [657, 890, 897]. Renal scarring may adversely affect renal growth and function, with bilateral scarring increasing the risk of insufficiency. Reflux nephropathy (RN) may be the most common cause of childhood hypertension. Follow-up studies have shown that 10-20% of children with RN develop hypertension or end-stage renal disease [898].

*3.14.2 **Diagnostic evaluation***

The diagnostic work-up should aim to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence of VUR, and LUT function. A basic diagnostic work-up comprises a detailed medical history (including family history, and screening for LUTD), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture, and serum creatinine in patients with bilateral renal parenchymal abnormalities.

The standard imaging tests include renal and bladder US, VCUG and nuclear renal scans. The criterion standard in diagnosis of VUR is VCUG, especially at the initial work-up. This test provides precise anatomical detail and allows grading of VUR [899]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR [900, 901] (Table 2). The grading system combines two earlier classifications and is based upon the extent of retrograde filling and dilatation of the ureter, renal pelvis and calyces on VCUG [901].

Radionuclide studies for detection of reflux have lower radiation exposure than VCUG, but the anatomical details depicted are inferior [902]. Recent studies on alternative imaging modalities for detection on VUR have yielded good results with voiding US and magnetic resonance VCUG [903-905]. Contrast

enhanced voiding urosonography with intravesical instillation of different ultrasound contrast agents has been shown to be highly sensitive giving comparable results with conventional VCUG while avoiding exposure to ionising radiation [459, 906]. However, despite the concerns about ionising radiation and its invasive nature, conventional VCUG still remains the gold standard because it allows better determination of the grade of VUR (in a single or duplicated kidney) and assessment of the bladder and urethral configuration.

Table 2: Grading system for VUR on VCUG, according to the International Reflux Study Committee [907]

Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

Dimercaptosuccinic acid is the best nuclear agent for visualising the cortical tissue and differential function between both kidneys. Dimercaptosuccinic acid is taken up by proximal renal tubular cells and is a good indicator of renal parenchyma function. In areas of acute inflammation or scarring, DMSA uptake is poor and appears as cold spots. Dimercaptosuccinic acid scans are therefore used to detect and monitor renal scarring. A baseline DMSA scan at the time of diagnosis can be used for comparison with successive scans later during follow-up [908]. Dimercaptosuccinic acid can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis [909]. Children with a normal DMSA scan during acute UTI have a low-risk of renal damage [909, 910].

Video-urodynamic studies are only important in patients in whom secondary reflux is suspected, such as those with spina bifida or boys in whom VCUG is suggestive of PUV. In the case of LUTS, diagnosis and follow-up can be limited to non-invasive tests (e.g. voiding charts, US, or uroflowmetry) [880]. Cystoscopy has a limited role in evaluating reflux, except for infravesical obstruction or ureteral anomalies that might influence therapy.

3.14.2.1 Infants presenting with prenatally diagnosed hydronephrosis

Ultrasound of the kidney and bladder is the first standard evaluation tool for children with prenatally diagnosed hydronephrosis. It is non-invasive and provides reliable information regarding kidney structure, size, parenchymal thickness and collecting system dilatation [911, 912].

Ultrasound should be delayed until the first week after birth because of early oliguria in the neonate. It is essential to evaluate the bladder, as well as the kidneys. The degree of dilatation in the collecting system under US, when the bladder is both full and empty, may provide significant information about the presence of VUR. Bladder wall thickness and configuration may be an indirect sign of LUTD and reflux. The absence of hydronephrosis on postnatal US excludes the presence of significant obstruction; however, it does not exclude VUR.

Monitoring with careful US avoids unnecessary invasive and irradiating examinations. The first two US scans within the first one to two months of life are highly accurate for defining the presence or absence of renal pathology. In infants with two normal, successive scans, VUR is rare, and if present it is likely to be low-grade [891, 913]. The degree of hydronephrosis is not a reliable indicator for the presence of VUR, even though cortical abnormalities are more common in high-grade hydronephrosis [873]. The presence of cortical abnormalities on US (defined as cortical thinning and irregularity, as well as increased echogenicity) warrants the use of VCUG for detecting VUR [873]. Dimercaptosuccinic acid provides more reliable and quantitative measurement of the degree of cortical abnormalities, first detected with US.

The use of VCUG is recommended in patients with US findings of bilateral high-grade hydronephrosis, duplex kidneys with hydronephrosis, ureterocele, ureteric dilatation, and abnormal bladders, because the likelihood of VUR is much higher. In all other conditions, the use of VCUG to detect reflux is optional [873, 893, 914-916].

When infants who are diagnosed with prenatal hydronephrosis become symptomatic with UTIs, further evaluation with VCUG should be considered [915]. Patients with severe hydronephrosis and those whose hydronephrosis is sustained or progressive, need further evaluation to exclude obstruction.

3.14.2.2 Siblings and offspring of reflux patients

The screening of asymptomatic siblings and offspring is controversial. Some authors think that early identification of children with VUR may prevent episodes of UTI and therefore renal scarring, whereas others think that screening asymptomatic individuals is likely to result in significant over-treatment of clinically insignificant VUR. In screened populations the prevalence of VUR is 27.4% in siblings and 35.7% in offspring [907]. The overall estimate for renal cortical abnormalities is 19.3% (11-54%), with 27.8% having renal damage in cohorts of symptomatic and asymptomatic children combined. In asymptomatic siblings only, the rate of renal damage is 14.4% (0-100%). Although early screening and therefore early diagnosis and treatment appears to be more effective than late screening in preventing further renal damage [873, 875, 917, 918], screening in all siblings and offspring cannot be recommended based on the available evidence. The lack of RCTs for screened patients to assess clinical health outcomes makes evidence-based guideline recommendations difficult.

3.14.2.3 Recommendations for paediatric screening of VUR

Recommendations	Strength rating
Inform parents of children with vesicoureteric reflux (VUR) that siblings and offspring have a high prevalence of VUR.	Strong
Use renal ultrasound (US) for screening of sibling(s).	Strong
Use voiding cystourethrography if there is evidence of renal scarring on US or a history of urinary tract infection.	Weak
Do not screen older toilet-trained children since there is no added value in screening for VUR.	Weak

3.14.2.4 Children with febrile urinary tract infections

A routine recommendation of VCUG at zero to two years of age after the first proven febrile UTI is the safest approach as the evidence for the criteria to selecting patients for reflux detection is weak. Children with febrile infections and abnormal renal US findings may have higher risk of developing renal scars and they should all be evaluated for reflux [462]. If reflux is diagnosed, further evaluation has traditionally consisted of a DMSA scan.

An alternative “top-down” approach is also an option, as suggested by several studies in the literature. This approach carries out an initial DMSA scan close to the time of a febrile UTI, to determine the presence of pyelonephritis, which is then followed by VCUG if the DMSA scan reveals kidney involvement. A normal DMSA scan with no subsequent VCUG will fail to identify VUR in 5-27% of cases, with the missed VUR presumably being less significant. In contrast, a normal DMSA scan with no VCUG avoids unnecessary VCUG in > 50% of those screened [452, 919-921].

3.14.2.5 Children with lower urinary tract symptoms and vesicoureteric reflux

Detection of LUTD is essential in treating children with VUR. It is suggested that reflux with LUTD resolves faster after LUTD correction, and that patients with LUTD are at higher risk for developing UTI and renal scarring [879, 922]. The co-existence of both conditions should be explored in any patient who has VUR. If there are symptoms suggestive of LUTD (e.g. urgency, wetting, constipation or holding manoeuvres), an extensive history and examination, including voiding charts, uroflowmetry and residual urine determination, will reliably diagnose underlying LUTD.

Among toilet-trained children, those with both LUTD and VUR are at higher risk of developing recurrent UTIs than children with isolated VUR [490].

In LUTD, VUR is often low-grade and US findings are normal, and there is no indication for performing VCUG in all children with LUTD, but the presence of febrile infections should be meticulously investigated. The co-existence of LUTD and VUR means it would be better to do a test covering both conditions, such as a VUDS. Any patient with LUTD and a history of febrile UTI should be investigated with a VUDS, if available. Furthermore, any child who fails standard therapy for LUTD should undergo urodynamic investigation. At this stage, combining a urodynamic study with VCUG is highly recommended.

3.14.3 ***Disease management***

There are two main treatment approaches: conservative (non-surgical and surgical).

3.14.3.1 Non-surgical therapy

The objective of conservative therapy is prevention of febrile UTI. It is based on the understanding that:

- Vesicoureteric reflux resolves spontaneously, mostly in young patients with low-grade reflux.
- Resolution is nearly 80% in VUR grades I and II and 30-50% in VUR grades III-V within four to five years of follow-up.

- Spontaneous resolution is low for bilateral high-grade reflux [923].
- Vesicoureteric reflux does not damage the kidney when patients are free of infection and have normal LUT function.
- There is no evidence that small scars can cause hypertension, renal insufficiency or problems during pregnancy. Indeed, these are possible only in cases of severe bilateral renal damage.
- The conservative approach includes watchful waiting, intermittent or continuous antibiotic prophylaxis, and bladder rehabilitation in those with LUTD [657, 922, 924-926].
- Circumcision during early infancy may be considered as part of the conservative approach because it is effective in reducing the risk of infection in normal children [927].

3.14.3.1.1 Follow-up

Regular follow-up with imaging studies (e.g. VCUG, nuclear cystography, or DMSA scan) is part of the conservative management to monitor spontaneous resolution and kidney status. Conservative management should be dismissed in all cases of febrile breakthrough infections, despite prophylaxis, and intervention should be considered.

3.14.3.1.2 Continuous antibiotic prophylaxis

Vesicoureteral reflux increases the risk of UTI and renal scarring especially when in combination with LUTD. Many prospective studies have evaluated the role of continuous antibiotic prophylaxis in the prevention of recurrent UTI and renal scarring.

It is clear that antibiotic prophylaxis may not be needed in every reflux patient [928-930]. Trials show the benefit of CAP is none or minimal in low-grade reflux. Continuous antibiotic prophylaxis is useful in patients with grade III and IV reflux in preventing recurrent infections but its use in preventing further renal damage is not proven. Toilet-trained children and children with LUTD derive better benefit from CAP [930-935]. The RIVUR trial was the largest, randomised, placebo-controlled, double blind, multi-centre study, involving 607 children aged 2-72 months with grade I-IV VUR. The RIVUR study showed that prophylaxis reduced the risk of recurrent UTI by 50% but not renal scarring and its consequences (hypertension and renal failure), at the cost of increased antimicrobial resistance. The benefit of prophylaxis was insignificant in patients with grade III or IV VUR and in the absence of LUTD [936-939]. Additional review of the RIVUR data based on a risk classification system defines a high-risk group (uncircumcised males; presence of BBD and high grade reflux) who would benefit from a antibiotic prophylaxis significantly. Therefore selective prophylaxis for this group is recommended [940].

It may be difficult and risky to select patients who do not need CAP. A safe approach would be to use CAP in most cases. Decision-making may be influenced by the presence of risk factors for UTI, such as young age, high-grade VUR, status of toilet-training/LUTS, female sex, and circumcision status. Although the literature does not provide any reliable information about the duration of CAP in reflux patients, a practical approach would be to use CAP until after children have been toilet-trained and ensuring that there is no LUTD. Continuous antibiotic prophylaxis is mandatory in patients with LUTD and reflux. Active surveillance of UTI is needed after CAP is discontinued. The follow-up scheme and the decision to perform an anti-reflux procedure or discontinuation of CAP may also depend on personal preferences and the attitude of patients and caregivers. It is strongly advised that the advantages and disadvantages should be discussed in detail with the family.

3.14.3.2 Surgical treatment

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral re-implantation.

3.14.3.2.1 Subureteric injection of bulking materials

With the availability of biodegradable substances, endoscopic subureteric injection of bulking agents has become an alternative to long-term antibiotic prophylaxis and open surgical intervention in the treatment of VUR in children. Using cystoscopy, a bulking material is injected beneath the intramural part of the ureter in a submucosal location. The injected bulking agent elevates the ureteral orifice and the distal ureter, so that coaptation is increased. This results in narrowing of the lumen, which prevents reflux of urine into the ureter, while still allowing its antegrade flow.

Several bulking agents have been used over the past two decades, including polytetrafluoroethylene (PTFE or Teflon™), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, a solution of dextranomer/hyaluronic acid (Deflux™, Dexell®) and more recently polyacrylatepolyalcohol copolymer hydrogel (Vantris®) [941, 942].

Although the best results have been obtained with PTFE [943], due to concerns about particle migration, PTFE has not been approved for use in children [944]. Although they are all biocompatible, other compounds such as collagen and chondrocytes have failed to provide a good outcome. Deflux™ was

approved by the USA FDA in 2001 for the treatment of VUR in children. Initial clinical trials have demonstrated that this method is effective in treating reflux [945]. Studies with long-term follow-up have shown that there is a high recurrence rate which may reach as high as 20% in two years [930]. In a meta-analysis [946] of 5,527 patients and 8,101 renal units, the reflux resolution rate (by ureter) following one treatment for grades I and II reflux was 78.5%, 72% for grade III, 63% for grade IV, and 51% for grade V. If the first injection was unsuccessful, the second treatment had a success rate of 68% and the third treatment 34%. The aggregate success rate with one or more injections was 85%. The success rate was significantly lower for duplicated (50%) vs. single (73%) systems, and neuropathic (62%) vs. normal (74%) bladders.

Obstruction at UVJ may happen in the long term follow-up after endoscopic correction of reflux. Patients with high-grade reflux and dilated ureters are at risk of late obstruction. It is significantly more common when polyacrylate-polyalcohol copolymer is used as bulking substance [947-949].

Clinical validation of the effectiveness of anti-reflux endoscopy is currently hampered by the lack of methodologically appropriate studies. In the most recent prospective, randomised trials comparing three treatment arms: i) endoscopic injection; ii) antibiotic prophylaxis; iii) surveillance without antibiotic prophylaxis in 203 children aged one to two years with grade III/IV reflux, endoscopic treatment gave the highest resolution rate of 71% compared to 39% and 47% for treatment arms ii and iii, respectively, after two years' follow-up. The recurrence rate at two years after endoscopic treatment was 20%. The occurrence of febrile UTIs and scar formation was highest in the surveillance group at 57% and 11%, respectively. New scar formation rate was higher with endoscopic injection (7%) compared with antibiotic prophylaxis (0%) [950]. Longer follow-up studies are needed to validate these findings.

3.14.3.2.2 Open surgical techniques

Various intra- and extravesical techniques have been described for the surgical correction of reflux. Although different methods have specific advantages and complications, they all share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. All techniques have been shown to be safe with a low rate of complications and excellent success rates (92-98%) [951].

The most popular and reliable open procedure is cross trigonal re-implantation described by Cohen [949]. The main concern with this procedure is the difficulty of accessing the ureters endoscopically, if needed, when the child is older. Alternatives are suprahiatal re-implantation (Politano-Leadbetter technique) and infrahiatal re-implantation (Glenn-Anderson technique). If an extravesical procedure (Lich-Gregoir) is planned, cystoscopy should be performed pre-operatively to assess the bladder mucosa and the position and configuration of the ureteric orifices. In bilateral reflux, an intravesical anti-reflux procedure may be considered, because simultaneous bilateral extravesical reflux repair carries an increased risk of temporary post-operative urine retention [952]. Overall, all surgical procedures offer very high and similar success rates for correcting VUR.

3.14.3.2.3 Laparoscopy and robot-assisted

There have been a considerable number of case series of transperitoneal, extravesical and pneumovesicoscopic intravesical ureteral re-implantation, which have shown the feasibility of the techniques. Various anti-reflux surgeries have been performed with the robot and the extravesical approach is the most commonly used. Although initial reports give comparable outcomes to their open surgical counterparts in terms of successful resolution of reflux, recent meta-analysis of results of Robotic-Assisted Laparoscopic Ureteral Reimplantation (RALUR) are within a wide range of variation and on average they are poor compared to open surgery. Operative times, costs and post-operative complications leading to secondary interventions are higher with RALUR but post-operative pain and hospital stay is less compared to open surgery [953-956].

Also, laparoscopic- or robotic-assisted approaches are more invasive than endoscopic correction and their advantages over open surgery are still debated. Therefore, at present, a laparoscopic approach cannot be recommended as a routine procedure. It can be offered as an alternative to the caregivers in centres where there is established experience [927, 957-965].

3.14.4 *Summary of evidence and recommendations for the management of vesicoureteric reflux in childhood*

Summary of evidence
There is no evidence that correction of persistent low-grade reflux (grades I-III) without symptoms and normal kidneys offers a significant benefit.
The traditional approach of initial medical treatment after diagnosis and shifting to interventional treatment in case of breakthrough infections and new scar formation needs to be challenged, because the treatment should be tailored to different risk groups.
Surgical correction should be considered in patients with persistent high-grade reflux (grades IV/V). There is no consensus about the timing and type of surgical correction. The outcome of open surgical correction is better than endoscopic correction for higher grades of reflux, whereas satisfactory results can be achieved by endoscopic injection for lower grades.
The choice of management depends on the presence of renal scars, clinical course, grade of reflux, ipsilateral renal function, bilaterality, bladder function, associated anomalies of the urinary tract, age, compliance, and parental preference. Febrile UTI, high-grade reflux, bilaterality, and cortical abnormalities are considered to be risk factors for possible renal damage. The presence of LUTD is an additional risk factor for new scars.

Recommendations	**Strength rating**
Initially treat all patients diagnosed within the first year of life with continuous antibiotic prophylaxis, regardless of the grade of reflux or presence of renal scars.	Weak
Offer immediate, parenteral antibiotic treatment for febrile breakthrough infections.	Strong
Offer definitive surgical or endoscopic correction to patients with frequent breakthrough infections.	Weak
Offer open surgical correction to patients with persistent high-grade reflux and endoscopic correction for lower grades of reflux.	Strong
Initially manage all children presenting at age one to five years conservatively.	Strong
Offer surgical repair to children above the age of one presenting with high-grade reflux and abnormal renal parenchyma.	Weak
Offer close surveillance without antibiotic prophylaxis to children presenting with lower grades of reflux and without symptoms.	Strong
Ensure that a detailed investigation for the presence of lower urinary tract dysfunction (LUTD) is done in all and especially in children after toilet-training. If LUTD is found, the initial treatment should always be for LUTD.	Strong
Offer surgical correction, if parents prefer definitive therapy to conservative management.	Strong
Select the most appropriate management option based on: • the presence of renal scars; • clinical course; • the grade of reflux; • ipsilateral renal function; • bilaterality; • bladder function; • associated anomalies of the urinary tract; • age and gender; • compliance; • parental preference. Refer to Table 3 for risk factors and follow-up.	Weak
In high-risk patients who already have renal impairment, a more aggressive, multidisciplinary approach is needed.	Strong

Table 3: Management and follow-up according to different risk groups

Risk Groups	Presentation	Initial treatment	Comment	Follow-up
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grades IV-V), abnormal kidneys and LUTD	Initial treatment is always for LUTD with CAP; intervention may be considered in cases of BT infections or persistent reflux	Greater possibility of earlier intervention	More aggressive follow-up for UTI and LUTD; full re-evaluation after 6 months
High	Symptomatic male or female patients after toilet-training with high-grade reflux (grade IV-V), abnormal kidneys and no LUTD	Intervention should be considered	Open surgery has better results than endoscopic surgery	Post-operative VCUG on indication only; follow-up of kidney status until after puberty
Moderate	Symptomatic male or female patients before toilet-training, with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT infections or persistent reflux	Spontaneous resolution is higher in males	Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Asymptomatic patients (PNH or sibling) with high-grade reflux and abnormal kidneys	CAP is the initial treatment. Intervention may be considered in cases of BT, infections or persistent reflux		Follow-up for UTI/ hydronephrosis; full re-evaluation after 12-24 months
Moderate	Symptomatic male or female patients after toilet-training, with high-grade reflux and normal kidneys with LUTD	Initial treatment is always for LUTD with CAP. Intervention may be considered in cases of BT infections or persistent reflux	In case of persistent LUTD, despite urotherapy, intervention should be considered. The choice of intervention is controversial	Follow-up for UTI and LUTD, kidney status; full re-evaluation after successful urotherapy
Moderate	Symptomatic male or female patients after toilet-training with low-grade reflux, abnormal kidneys with or without LUTD	Choice of treatment is controversial. Endoscopic treatment may be an option. LUTD treatment should be given if needed		Follow-up for UTI, LUTD, and kidney status until after puberty
Moderate	All symptomatic patients with normal kidneys, with low-grade reflux, with LUTD	Initial treatment is always for LUTD with or without CAP		Follow-up for UTI and LUTD
Low	All symptomatic patients with normal kidneys, with low-grade reflux, with no LUTD	No treatment or CAP	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI
Low	All asymptomatic patients with normal kidneys with low-grade reflux	No treatment or CAP in infants	If no treatment is given, parents should be informed about risk of infection	Follow-up for UTI

BT = breakthrough; CAP = continuous antibiotic prophylaxis; LUTD = lower urinary tract dysfunction; PNH = prenatal diagnosed hydronephrosis; UTI = urinary tract infection; VCUG = voiding cystourethrography.

3.15 Urinary stone disease

*3.15.1 **Epidemiology, aetiology and pathophysiology***

Paediatric stone disease is an important clinical problem in paediatric urology practice. Due to its recurrent nature, every effort should be made to discover the underlying metabolic abnormality so that it can be treated appropriately. Obtaining a stone-free state with close follow-up are of the utmost importance, although, it may not be possible in some circumstances (e.g. oxalosis or nephrocalcinosis).

Bladder stones are still common in underdeveloped areas of the world and are usually ammonium acid urate and uric acid stones, strongly implicating dietary factors [966]. Patients with augmented bladder constitute another important group with a risk of up to 15% [967].

The incidence and characteristics of stones show a wide geographical variation in children. Although urinary stone disease is generally considered to be a relatively rare disease, it is quite common in some parts of the world. Paediatric stone disease is endemic in Turkey, Pakistan and in some South Asian, African and South American countries. However, recent epidemiological studies have shown that the incidence of paediatric stone disease is also increasing in the Western world [968-970], especially in girls, Caucasian ethnicity, African Americans and older children [971]. More than 70% of stones in children contain calcium oxalate, while infection stones are found more frequently in younger children [972].

*3.15.2 **Classification systems***

Urinary stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection.

3.15.2.1 Calcium stones

Calcium stones are usually made from calcium oxalate or calcium phosphate. Super-saturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesemia) play a major role in the formation of calcium oxalate stones. Higher super-saturations of calcium oxalate was shown to be associated with multiple stone disease [973].

Hypercalciuria: This is defined by a 24-hour urinary calcium excretion of more than 4 mg/kg/day (0.1 mmol/kg/ day) in a child weighing < 60 kg. In infants younger than three months, 5 mg/kg/day (0.125 mmol/kg/day) is considered to be the upper limit for normal calcium excretion [974].

Hypercalciuria can be classified as either idiopathic or secondary. Idiopathic hypercalciuria is diagnosed when clinical, laboratory, and radiographic investigations fail to delineate an underlying cause leading to hypercalcaemia. Urinary calcium may increase in patients with high sodium chloride intake.

Secondary hypercalciuria occurs when a known process produces excessive urinary calcium. In secondary hypercalcaemic hypercalciuria, a high serum calcium level may be due to increased bone resorption (hyperparathyroidism, hyperthyroidism, immobilisation, acidosis, metastatic disease) or gastrointestinal hyperabsorption (hypervitaminosis D) [975].

A good screening test for hypercalciuria compares the ratio of urinary calcium to creatinine. The normal calcium-to-creatinine ratio in children is less than 0.2. If the calculated ratio is higher than 0.2, repeat-testing is indicated. Neonates and infants have a higher calcium excretion and lower creatinine excretion than older children [974, 975]. If the follow-up ratios are normal, then no additional testing for hypercalciuria is needed.

However, if the ratio remains elevated, a timed 24-hour urine collection should be obtained and the calcium excretion calculated.

The 24-hour calcium excretion test is the standard criterion for the diagnosis of hypercalciuria. If calcium excretion is higher than 4 mg/kg/day (0.1 mmol/kg/day), the diagnosis of hypercalciuria is confirmed and further evaluation is warranted: levels of serum bicarbonate, creatinine, alkaline phosphatase, calcium, phosphorus, magnesium, pH, and parathyroid hormone. Freshly voided urine should be measured for pH [974-976]. In addition to calcium, the 24-hour urine analysis should also include phosphorus, sodium, magnesium, uric acid, citrate and oxalate.

Initial management is always to increase fluid intake and urinary flow. Dietary modification is a mandatory part of effective therapy. The child should be referred to a dietician to assess accurately the daily intake of calcium, animal protein, and sodium. Dietary sodium restriction is recommended as well as maintenance of calcium intake consistent with the daily needs of the child [977]. A brief trial of a low calcium diet can be carried out to determine if exogenous calcium intake and/or calcium hyperabsorption is contributing to high urinary calcium. Any recommendation to restrict calcium intake below the daily needs of the child should be avoided. Moreover, low calcium intake is a risk factor for stone formation [978] (LE: 3).

Hydrochlorothiazide and other thiazide-type diuretics may be used to treat idiopathic hypercalciuria, especially with calcium renal leak, at a starting dosage of 0.5-1 mg/kg/day [979-982] (LE: 3). In long-term use of thiazide-type diuretics, a decrease in hypocalciuric effect may be seen after the third month and may cause hypokalemia, hypocitraturia, hyperuricaemia and hypomagnesaemia. Therefore, control of blood and serum values should be performed with regular intervals. Citrate therapy is also useful if citrate levels are low or if hypercalciuria persists, despite other therapies [979, 983] (LE: 4).

Hyperoxaluria: Only 10-15% of oxalate comes from diet.
The average child excretes less than 50 mg (0.57 mmol)/1.73 m2/day [984-986], while infants excrete four times as much. Hyperoxaluria may result from increased dietary intake, enteric hyperabsorption (as in short bowel syndrome) or an inborn error of metabolism.

In rare primary hyperoxaluria, one of the two liver enzymes that play a role in the metabolism of oxalate may be deficient. With increased deposition of calcium oxalate in the kidneys, renal failure may ensue in resulting deposition of calcium oxalate in other tissues (oxalosis). The diagnosis is made upon laboratory findings of severe hyperoxaluria and clinical symptoms. The definitive diagnosis requires liver biopsy to assay the enzyme activity.

Other forms of hyperoxaluria, as mentioned earlier, may be due to hyperabsorption of oxalate in inflammatory bowel syndrome, pancreatitis and short bowel syndrome. Yet, the majority of children have 'mild' (idiopathic) hyperoxaluria, with urine oxalate levels elevated only mildly in these cases. The treatment of hyperoxaluria consists of the promotion of high urine flow, restriction of dietary oxalate and regular calcium intake. Pyridoxine may be useful in reducing urine levels, especially in primary hyperoxaluria. Citrate administration increases inhibitory urine activity [979, 987] (LE: 4).

Hypocitraturia: Citrate is a urinary stone inhibitor. Citrate acts by binding to calcium and by directly inhibiting the growth and aggregation of calcium oxalate as well as calcium phosphate crystals. Thus low urine citrate may be a significant cause of calcium stone disease. In adults, hypocitraturia is the excretion of citrate in urine of less than 320 mg/day (1.5 mmol/day) for adults; this value must be adjusted for children depending on body size [988-990].

Hypocitraturia usually occurs in the absence of any concurrent symptoms or any known metabolic derangements. It may also occur in association with any metabolic acidosis, distal tubular acidosis or diarrhoeal syndromes.

Environmental factors that lower urinary citrate include a high protein intake and excessive salt intake. Many reports emphasise the significance of hypocitraturia in paediatric calcium stone disease. The presence of hypocitraturia ranges from 30% to 60% in children with calcium stone disease [989, 991]. The urine calcium-to-citrate ratios were higher in recurrent calcium stone forming children than solitary formers [988, 992].

The restoration of normal citrate levels is advocated to reduce stone formation, although there are few relevant studies in children. Hypocitraturia is treated by potassium citrate at a starting dose of 1 mEq/kg, given in two divided doses [980] (LE: 3). The side effects of potassium citrate are very rare and most of the time they include non-specific gastrointestinal complaints. Potassium citrate should be used with caution in hyperkalemic and chronic renal failure conditions.

3.15.2.2 Uric acid stones

Uric acid stones are responsible for urinary calculi in 4-8% of children. Uric acid is the end product of purine metabolism. Hyperuricosuria is the main cause of uric acid stone formation in children. A daily output of uric acid of more than 10 mg/kg/day (0.6 mmol/kg/day) is considered to be hyperuricosuria [979].

The formation of uric acid stones is mainly dependent on the presence of acidic urinary composition. Uric acid dissociation and solubility is strongly reduced at pH of < 5.8. As the pH becomes more alkaline, uric acid crystals become more soluble and the risk of uric acid stone formation is reduced.

In the familial or idiopathic form of hyperuricosuria, children usually have normal serum uric acid levels. In other children, it can be caused by uric acid overproduction secondary to inborn errors of metabolism, myeloproliferative disorders or other causes of cell breakdown. Hyperuricosuria is also caused by high purine and protein intake. Although hyperuricosuria is a risk factor for calcium oxalate stone formation in adults, this does not appear to be a significant risk factor in children. Uric acid stones are non-opaque stones. Plain X-rays are insufficient to show uric acid stones, and renal sonography and spiral CT are used for diagnosis. Alkalinisation of urine is the mainstay of therapy and prevention for uric acid stones. Citrate preparations are useful as alkalinising agents. Maintaining a urine pH of 6 to 6.5 is sufficient to prevent uric acid stones [979]. In patients who failed with conservative measures with sustaining hyperuricosuria and

hyperuricemia, stone recurrences or myeloproliferative diseases, allopurinol (10 mg/kg) may be used. This medication may cause several drug reactions (rash, diarrhoea, eosinophilia) and should be cautiously used in chronic renal failure patients.

3.15.2.3 Cystine stones

Cystinuria is the cause of cystine stone formation and accounts for 2-6% of all urinary stones in children. Cystinuria is an incompletely recessive autosomal disorder characterised by failure of renal tubules to reabsorb four basic amino acids: cystine, ornithine, lysine and arginine.

Of these four amino acids, only cystine has poor solubility in urine, so that only cystine stones may form in the case of excessive excretion in urine. Cystine solubility is pH-dependent, with cysteine precipitation beginning at pH levels < 7.0. Other metabolic conditions, such as hypercalciuria, hypocitraturia and hyperuricosuria, may accompany cystinuria, so leading to the formation of mixed-composition stones. Cystine stones are faintly radiopaque and may be difficult to visualise on regular radiograph studies. They are also hard in texture and more difficult to disintegrate by extracorporeal shockwave lithotripsy (SWL). Cystinuric patients present with larger stones at the time of diagnosis, higher new stone formation rates, and are at higher risk of surgery [993].

The medical treatment for cystine stones aims to reduce cystine saturation in urine and increase its solubility. The initial treatment consists of maintaining a high urine flow and the use of alkalinising agents, such as potassium citrate to maintain urine pH at above 7.0 (better above 7.5). If this treatment fails, the use of α-mercaptopropionyl glycine or D-penicillamin may increase cystine solubility and reduce cystine levels in urine and prevent stone formation. Side effects of these drugs are mostly mild and include gastrointestinal complaints (alterations in taste and odour), fever and rash, however they can be associated with severe sideeffects, such as bone marrow depression, nephrotic syndrome and epidermolysis [994] (LE: 4).

3.15.2.4 Infection stones (struvite stones)

Infection-related stones constitute nearly 5% of urinary stones in children, though incidence increases over 10% in younger ages [995] and in non-endemic regions [972, 996]. Bacteria capable of producing urease enzyme (*Proteus, Klebsiella, Pseudomonas*) are responsible for the formation of such stones.

Urease converts urea into ammonia and bicarbonate, alkalinising the urine and further converting bicarbonate into carbonate. In the alkaline environment, triple phosphates form, eventually resulting in a supersaturated environment of magnesium ammonium phosphate and carbonate apatite, which in turn leads to stone formation.

In addition to bacterial elimination, stone elimination is essential for treatment, as stones will harbour infection and antibiotic treatment will not be effective. Consideration should be given to investigating any congenital problem that causes stasis and infection. Genitourinary tract anomalies predispose to formation of such stones.

3.15.3 ***Diagnostic evaluation***

Presentation tends to be age-dependent, with symptoms such as flank pain and haematuria being more common in older children. Non-specific symptoms (e.g. irritability, vomiting) are common in very young children. Haematuria, usually visible, occurring with or without pain, is less common in children. However, nonvisible haematuria may be the sole indicator and is more common in children. In some cases, urinary infection may be the only finding leading to radiological imaging in which a stone is identified [997, 998].

3.15.3.1 Imaging

Generally, US should be used as a first approach. Renal US is very effective for identifying stones in the kidney. Many radiopaque stones can be identified with a simple abdominal flat-plate examination. The most sensitive test for identifying stones in the urinary system (especially for ureteric stones) is non-contrast helical CT scanning. It is safe and rapid, with 97% sensitivity and 96% specificity [999-1001] (LE: 2). Despite its high diagnostic accuracy, because of the potential radiation hazards, its use should be reserved for cases with noninformative US and/or plain abdominal roentgenogram. Low dose protocols have also been developed with the goal of reducing radiation dose with adequate image quality [1002]. Intravenous pyelography is rarely used in children, but may be needed to delineate the caliceal anatomy prior to percutaneous or open surgery.

3.15.3.2 Metabolic evaluation

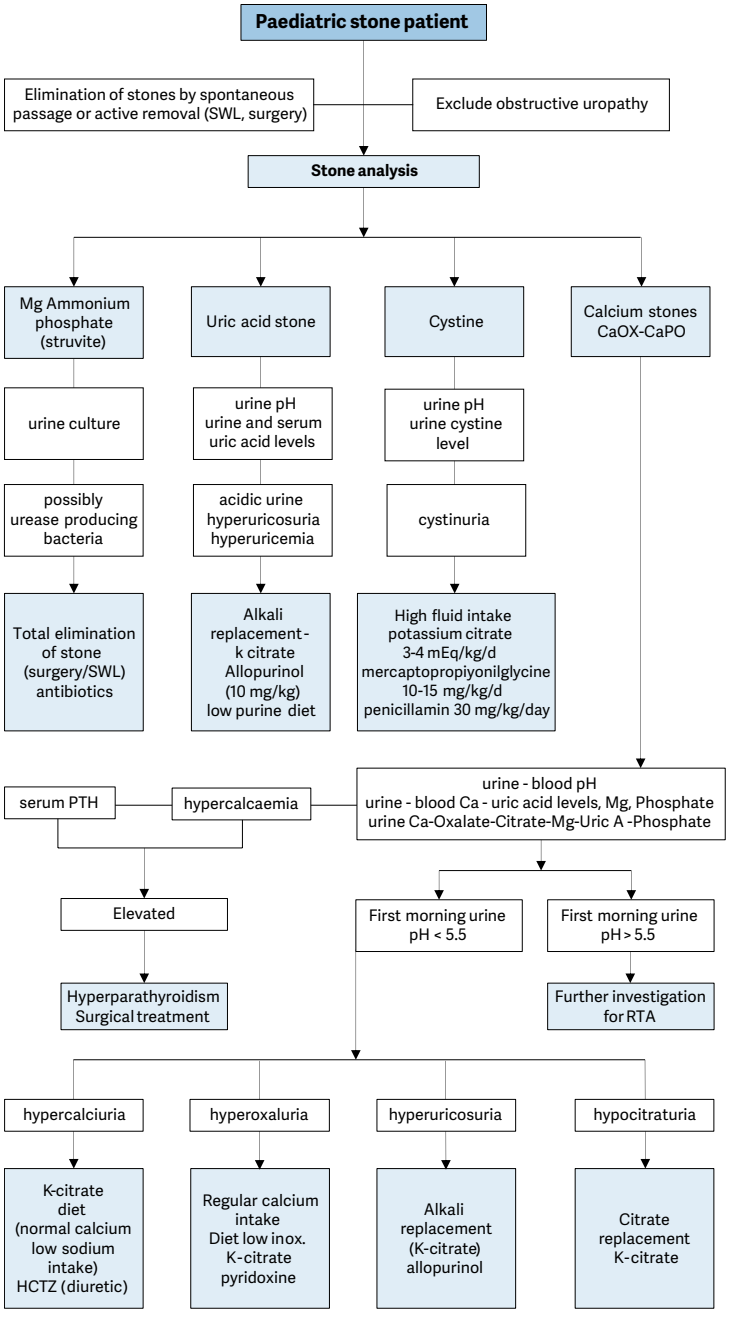
Due to the high incidence of predisposing factors for urolithiasis in children and high stone recurrence rates, every child with a urinary stone should be given a complete metabolic evaluation [966, 994, 1003, 1004]. A limited urinary metabolic evaluation (24-h calcium, citrate, and oxalate and low urinary volume) is able to detect the vast majority of clinically significant metabolic abnormalities [1005]. However collections are most of the time inadequate and should be repeated in this case [1005, 1006].

Metabolic evaluation includes:

- family and patient history of metabolic problems and dietary habits;
- analysis of stone composition (following stone analysis, metabolic evaluation can be modified according to the specific stone type);
- electrolytes, blood/urea/nitrogen (BUN), creatinine, calcium, phosphorus, alkaline phosphatase, uric acid, total protein, carbonate, albumin, and parathyroid hormone (if there is hypercalcaemia);
- spot urinalysis and culture, including ratio of calcium to creatinine;
- urine tests, including a 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, protein, and creatinine clearance;
- 24-hour cystine analysis if cystinuria is suspected (positive sodium nitroprusside test, cystine stone, cystine hexagonal crystals in urine).

Figure 10 provides an algorithm of how to perform metabolic investigations in urinary stone disease in children and how to plan medical treatment accordingly.

Figure 10: Algorithm for metabolic investigations in urinary stone disease in children


Paediatric stone patient
Elimination of stones by spontaneous passage or active removal (SWL, surgery)
Exclude obstructive uropathy
Stone analysis
Mg Ammonium phosphate (struvite)
Uric acid stone
Cystine
Calcium stones CaOX-CaPO
urine culture
urine pH urine and serum uric acid levels
urine pH urine cystine level
possibly urease producing bacteria
acidic urine hyperuricosuria hyperuricemia
cystinuria
Total elimination of stone (surgery/SWL) antibiotics
Alkali replacement - k citrate Allopurinol (10 mg/kg) low purine diet
High fluid intake potassium citrate 3-4 mEq/kg/d mercaptopropiyonilglycine 10-15 mg/kg/d penicillamin 30 mg/kg/day
urine - blood pH urine - blood Ca - uric acid levels, Mg, Phosphate urine Ca-Oxalate-Citrate-Mg-Uric A -Phosphate
serum PTH
hypercalcaemia
Elevated
Hyperparathyroidism Surgical treatment
First morning urine pH < 5.5
First morning urine pH > 5.5
Further investigation for RTA
hypercalciuria
hyperoxaluria
hyperuricosuria
hypocitraturia
K-citrate diet (normal calcium low sodium intake) HCTZ (diuretic)
Regular calcium intake Diet low inox. K-citrate pyridoxine
Alkali replacement (K-citrate) allopurinol
Citrate replacement K-citrate

Ca = calcium; HCTZ = hydrochlorothiazide; Mg = magnesium; Ox = oxalate; PTH = parathyroid hormone; SWL = extracorporeal shockwave lithotripsy; RTA = renal tubular acidosis; Uric A = uric acid.

3.15.4 ***Management***

Adequate fluid intake and restricting the use of salt within daily allowance range are the general recommendations besides the specific medical treatment against the detected metabolic abnormalities. With the advance of technology, stone management has changed from open surgical approaches to endoscopic techniques that are less invasive. Deciding on the type of treatment depends on the number, size, location, stone composition and the anatomy of the urinary tract [1004, 1007, 1008]. Expectant management is the initial management in children with asymptomatic small size stones (< 4-5 mm) with a possibility of spontaneous clearance. There is no consensus on the size of stones for different ages eligible for clearance and the duration of conservative follow-up. Adult literature reveals the benefits of medical expulsive therapy (MET) using α-blockers. Although, experience in children is limited showing different results [1009], a meta-analysis of three randomised and two retrospective studies demonstrate that treatment with MET results in increased odds of spontaneous ureteral stone passage and a low rate of adverse events [1010]. Currently, most paediatric stones can easily be managed by SWL. Endoscopic treatment can be applied for ureteric and bladder stones. Percutaneous removal of stones is also possible for kidney stones in children. Only a small portion of children will require open surgery but all attempts must be made to completely remove all stones since post-operative residual fragments pass spontaneously in only 20-25% of cases [1011, 1012]. A congenital obstructive uropathy should be managed together with stone removal therapy to prevent recurrence.

3.15.4.1 Extracorporeal shockwave lithotripsy

Many reports confirm that SWL can be performed in children with no suspicion of long-term morbidity of the kidney [1013-1020].

The mean number of shockwaves for each treatment is approximately 1,800 and 2,000 (up to 4,000 if needed) and the mean power settings vary between 14 kV and 21 kV. The use of US and digital fluoroscopy has significantly decreased the radiation exposure and it has been shown that children are exposed to significantly lower doses of radiation compared to adults [1007, 1021, 1022]. Concerns about anaesthesia no longer present a problem due to advances in technique and medication, even in the infant age group. The type of anaesthesia should be general or dissociative for children under ten years of age, whereas conventional intravenous sedation or patient-controlled analgesia is an option for older children who are able to co-operate [1023] (LE: 2b).

Stone-free rates are significantly affected by various factors. Regardless of the location, as the stone size increases, the stone-free rates decrease and retreatment rate increases. The stone-free rates for < 1 cm, 1-2 cm, > 2 cm and overall, were reported as nearly 90%, 80%, 60% and 80%, respectively. As the stone size increases, the need for additional sessions increases [1007, 1021, 1022, 1024-1028].

Localisation of the calculi has been described as a significant factor affecting the success rates in different studies. Stones in the renal pelvis and upper ureter seem to respond better to SWL. For these locations, the stone clearance rates are nearly 90%. However, SWL was found to be less effective for caliceal stones; particularly the lower caliceal stones. Several studies reported stone-free rates for isolated lower caliceal stones varying between 50% and 62% [1029-1031].

Shockwave lithotripsy can also be used to treat ureteral calculi. However, this is a more specific issue and controversial. The success rates with SWL are less for distal ureteric stones. There may also be technical problems with localisation and focusing of ureteric stones in children [1030-1033].

The type of machine used significantly influences success rates and complications. First-generation machines can deliver more energy to a larger focal zone, resulting in higher fragmentation rates in a single therapy. However, general anaesthesia is usually required due to the intolerable discomfort associated with a first-generation machine. Later-generation machines have a smaller focal zone and deliver less energy, and have a lower risk of pulmonary trauma, however, additional treatments may be needed. The success rate is higher in younger children [1026].

Although stenting does not affect stone clearance, overall complication rates are higher and hospital stay is longer in the unstented patient [1026, 1028]. Stenting is essential in solitary kidneys undergoing SWL treatment. Children with a large stone burden have a high risk of developing Steinstrasse and urinary obstruction and should be followed more closely for the risk of prolonged urinary tract obstruction after SWL. Post-SWL stent or nephrostomy tube placement may be needed in prolonged obstruction [994, 1025].

The Hounsfield Unit (HU) of stone on non-contrast tomography has also been shown to be a predictive factor for success in children and SWL was found to be more successful in stones with HU less than 600 [1012] and 1,000 [1034]. Two nomogram studies revealed male gender, younger age, smaller stone size, single stone, non-lower pole localisation and negative history for previous intervention are favourable factors for stone clearance in paediatric SWL [1035, 1036]. A recent comparative study reported that these two nomograms are independent predictors of stone-free rate following SWL in paediatric patients [1037]. Although, the invention of miniaturised endoscopic instruments seems to reduce the importance and popularity of SWL, it has the advantage of not carrying the risk of certain complications related to endoscopic surgeries

and moreover studies comparing SWL and RIRS showed that besides having similar stone-free rates, SWL was cheaper, had shorter hospital stay [1038], with less post-operative emergency visit, pain and anaesthetic session [1039]. Complications arising from SWL in children are usually self-limiting and transient. The most common are:

- renal colic;
- transient hydronephrosis;
- dermal ecchymosis;
- UTI;
- formation of Steinstrasse;
- sepsis;
- rarely, haemoptysis.

In children with sterile pre-operative urine cultures, antibiotic prophylaxis to decrease infectious complications is not recommended [1040]. However, every effort should be made to sterilise the urine before performing SWL, ureteroscopy (URS), or percutaneous nephrolithotomy (PCNL).

Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [1041-1050].

3.15.4.2 Percutaneous nephrolithotomy

Shockwave lithotripsy is the first choice for treating most renal paediatric stones. However, percutaneous renal surgery should be used for larger and complex stones. Pre-operative evaluation, indication and surgical technique are similar in children and adults. In most cases, percutaneous nephrolithotomy (PCNL) is used as monotherapy, but is also used as an adjunctive procedure to other therapies.

The use of adult-sized instruments, in association with an increased number of tracts and sheath size, seems to increase blood loss. However, the development of small-calibre instruments means that PCNL can be used in children. In children (particularly smaller children), PCNL has some advantages, such as smaller skin incision, single-step dilation and sheath placement, good working access for paediatric instruments, variable length, and lower cost [1040, 1051, 1052].

As monotherapy, PCNL is considerably effective and safe. The reported stone-free rates in the recent literature are between 86.9% and 98.5% after a single session. These rates increase with adjunctive measures, such as second-look PCNL, SWL and URS. Even in complete staghorn cases, a clearance rate of 89% has been achieved following a single session [1044, 1053-1057].

The most frequently reported complications of PCNL in children are bleeding, post-operative fever or infection, and persistent urinary leakage. Bleeding requiring transfusion in the modern series is reported in less than 10% [1058-1063] and is closely associated with stone burden, operative time, sheath size and the number of tracts [1062, 1064, 1065]. In recent studies, post-operative infectious complications, such as fever with or without documented UTI, are reported as less than 15% [1058, 1059, 1061-1063, 1066] and the origin of fever is not always found to be the infection. With the availability of smaller size instruments, miniaturised PCNL ('miniperc') through a 13F or 14F sheath [1052, 1066, 1067] as well as ultramini-PCNL (UMP) through 12F sheaths [1068] have become possible, with decreased transfusion rates [1066]. The mini- and supermini-PCNL (SMP) were shown to have higher efficacy with acceptable complication rates which were deemed to be a safe alternative to SWL by some authors [1069, 1070]. The SMP was shown to be advantageous over mini-PCNL in terms of complications with similar stone-free rates [1071, 1072]. This miniaturisation has been further developed into the technique of 'micro-perc' using a 4.85F 'all-seeing needle'. This technique is still experimental and enables the stone to be fragmented by a laser *in situ* and left for spontaneous passage [1073]. A study revealed that microperc provides a similar stone-free rate with similar complication rates and a lower additional treatment rate compared with SWL in the treatment of kidney stone disease in children [1074] (LE: 3). For stones 10-20 mm, micro-PNL was shown to have comparable results, with less bleeding, compared to mini-PCNL [1075] and similar outcomes with less anaesthetic sessions compared to RIRS [1076] (LE: 3). As experience has accumulated in adult cases, new approaches have started to be applied in children, including tubeless PCNL. This technique has been used in uncomplicated surgery for stones < 2 cm, with patients left either with an indwelling catheter or double J stent in the ureter [1060, 1077] or totally tubeless [1078]. Moreover, use of US for establishment of access is gaining popularity [1079, 1080] and supine approach [1081] was also reported to be feasible in children.

The mean post-operative hospital stay is similar to adults. It is reported as three to four days in all published literature and is much shorter than open surgery. The less invasive nature of this technique has made it a promising alternative to open surgery for treating renal stones in children (LE: 2) [1058, 1060, 1061, 1063-1065, 1067, 1068, 1073-1075, 1077, 1078, 1081, 1082].

3.15.4.3 Ureterorenoscopy

The increasing availability of smaller size endourological equipment has made it possible to manage paediatric ureteral stones using endoscopic techniques.

The technique used in children is similar to the one used in adults. It is strongly recommended that guide wires are used and the procedure is performed using direct vision. Routine balloon dilation of the ureterovesical junction and ureteral stenting are controversial. In general, ureteric dilatation is being performed less and only in selected cases. There is a tendency to use hydrodilation more because it is similarly effective [1, 1040, 1042, 1048, 1083-1086] (LE: 3).

Different lithotripsy techniques, including ultrasonic, pneumatic and laser lithotripsy, have all been shown to be safe and effective. Due to the smaller size of the probes, laser energy is easier to use in smaller instruments and is more useful for paediatric cases [1041-1050].

All studies reporting the use of endoscopy for ureteric stones in children have clearly demonstrated that there is no significant risk of ureteric strictures or reflux with this mode of therapy (LE: 1). The risk of post-operative hydronephrosis depends on the presence of impacted stone and ureteral injury during operation [1087]. A multi-institutional study on the use of semi-rigid ureteroscopy for ureteral calculi in children has revealed that the procedure is effective with a 90% stone-free rate and efficacy quotient. The study also focused on the factors affecting the complication rates. The authors found that, although operating time, age, institutional experience, orifice dilation, stenting and stone burden were significant on univariate analysis, multivariate analysis revealed that operating time was the only significant parameter affecting the complication rate [1088]. However, for proximal ureteral stones semi-rigid ureteroscopy is not a good first option because of higher complication and failure rates [1089].

A recent literature review contains a growing number of case series on the use of flexible ureterorenoscopic interventions in children. Both intrarenal and ureteric stones can be treated using this approach [1090-1095]. In these series, the authors generally did not use active orifice dilation, but attempted to use a ureteral sheath where possible. However, an important problem was the inability to obtain retrograde access to the ureter in approximately half of the cases [1091, 1093]. This problem can be overcome by stenting and leaving the stent indwelling for passive dilation of the orifice, and performing the procedure in a second session. The success rates varied between 60 and 100%, with a negligible number of complications [1090, 1092-1094, 1096]. The need for additional procedures was related to stone size [1094]. A comparative study showed that retrograde intra-renal surgery (RIRS) had similar stone-free rate compared to ESWL after three months, with fewer sessions [1097], however for stones larger than 2 cm, RIRS monotherapy has lower stonefree rates than mini-PCNL with the advantages of decreased radiation exposure, fewer complications and shorter hospital stay [1098] (LE: 3). In contrast, for stones between 10-20 mm, RIRS has similar success and complication rates and shorter hospital stay and low radiation exposure when compared to micro-PNL [1099] (LE: 3). A recent systematic review revealed that compared with the other two treatments, PCNL had a longer operative time, fluoroscopy time and hospital stay. Shockwave lithotripsy had a shorter hospital stay, higher retreatment rate and auxiliary rate in comparison with the other two treatments. It was also shown that PCNL presented a higher efficacy quotient than the other two treatments, and RIRS had a lower efficiency than SWL and PCNL. In the subgroup analysis of paediatric patients with stone ≤ 20 mm, the comparative results were similar to those described above, except for the higher complication rate of PCNL than SWL [1100].

3.15.4.4 Open or laparoscopic stone surgery

Most stones in children can be managed by SWL and endoscopic techniques. However, in some situations, open surgery is inevitable. Good candidates for open stone surgery include very young children with large stones and/or a congenitally obstructed system, which also require surgical correction. Open surgery is also necessary in children with severe orthopaedic deformities that limit positioning for endoscopic procedures.

In centres with a well-established experience, a laparoscopic approach may be a good alternative for some cases as a last resort before open surgery. Suitable candidates include patients who have a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant UPJ obstruction or caliceal diverticula, mega-ureter, or large impacted stones. Laparoscopic stone surgery via conventional or a robot-assisted transperitoneal or retroperitoneal approach can be attempted. However, there is limited experience with these techniques and they are not routine therapeutic modalities [1101-1104].

Bladder stones in children can usually be managed by endoscopic techniques. Open surgery may also be used for very large bladder stones or for bladder stones caused by an anatomical problem.

In addition to the advantages and disadvantages of each treatment modality for the specific size and location of the stone, consideration has to be given to the availability of the instruments and the experience with each treatment modality before the choice of technique is made. Recommendations for interventional management are given in Table 4.

Table 4: Recommendations for interventional management in paediatric stones

Stone size and localisation*	Primary treatment option	Secondary treatment options	Comment
Staghorn stones	PCNL	Open/SWL	Multiple sessions and accesses with PCNL may be needed. Combination with SWL may be useful.
Pelvis < 10 mm	SWL	RIRS/PCNL/MicroPerc	
Pelvis 10-20 mm	SWL	PCNL/RIRS	Multiple sessions with SWL may be needed. PCNL has similar recommendation grade.
Pelvis > 20 mm	PCNL	PCNL MicroPerc/ Open	Multiple sessions with SWL may be needed.
Lower pole calyx	PCNL	SWL/Open	Multiple sessions with SWL may be needed.
< 10 mm	SWL	SWL/Open	Anatomical variations are important for complete clearance after SWL.
Lower pole calyx	SWL	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
> 10 mm	PCNL	RIRS/PCNL/MicroPerc	Anatomical variations are important for complete clearance after SWL.
Upper ureteric stones	SWL	SWL/ MicroPerc	
Lower ureteric stones	URS	PCNL/URS/Open	Additional intervention need is high with SWL.
Bladder stones	Endoscopic	SWL/Open	Open is easier and with less operative time with large stones.
Bladder stones	Endoscopic		Open is easier and with less operative time with large stones.

** Cystine and uric acid stones excluded.*
PCNL = percutaneous nephrolithotomy; SWL = shockwave lithotripsy; RIRS = retrograde intrarenal surgery; URS = ureteroscopy.

3.15.5 Summary of evidence and recommendations for the management of urinary stones

Summary of evidence	LE
The incidence of stone disease in children is increasing.	2
Contemporary surgical treatment is based on minimally invasive modalities. Open surgery is very rarely indicated.	2a
The term 'clinically insignificant residual fragments' is not appropriate for children since most of them become symptomatic and require intervention.	2b

Recommendations	LE	Strength rating
Use plain abdominal X-ray and ultrasound as the primary imaging techniques for the diagnosis and follow-up of stones.	2b	Strong
Use low-dose non-contrast computed tomography in cases with a doubtful diagnosis, especially of ureteral stones or complex cases requiring surgery.	2a	Strong
Perform a metabolic evaluation in any child with urinary stone disease. Any kind of interventional treatment should be supported with medical treatment for the underlying metabolic abnormality, if detected.	2a	Strong
Limit open surgery under circumstances in which the child is very young with large stones, in association with congenital problems requiring surgical correction and/or with severe orthopaedic deformities that limit positioning for endoscopic procedures.	2a	Strong

3.16 Obstructive pathology of renal duplication: ureterocele and ectopic ureter

*3.16.1 **Epidemiology, aetiology and pathophysiology***

Ureterocele and ectopic ureter are the two main anomalies associated with complete renal duplication, but they also occur in a single system. At present, antenatal US detects both conditions in the majority of cases if associated with obstruction, and diagnosis is confirmed after birth by further examination. Later in life, these anomalies are revealed by clinical symptoms: UTI, pain, calculus formation, disturbances of micturition, and urinary incontinence. There is a wide variation of symptoms in patients with ureterocele (from the asymptomatic patient to urosepsis, urinary retention and upper tract dilatation after birth).

3.16.1.1 Ureterocele

Ureterocele is four to seven times more frequent in female than in male patients; the overall incidence in autopsies is around one in 4,000 children. Around 80% is associated with the upper pole ureter in duplicated systems and 20% in single systems. About 10% of ureteroceles are bilateral [1105].

3.16.1.2 Ectopic ureter

Ectopic ureter is less frequent than ureterocele (10 in 19,046 autopsies), but is also more common in female patients (male to female ratio is 1:5). Some remain asymptomatic, therefore, the true incidence is difficult to determine [1106]. Eighty per cent of ectopic ureters are associated with complete renal duplication; however, in male patients about 50% of ectopic ureters are associated with a single system [1107]. The incidence of ectopic ureter is 3.5% in patients with anorectal malformations [1108].

3.16.2 Classification systems

3.16.2.1 Ureterocele

Ureterocele is a cystic dilatation that develops in the intravesical part of the submucosal ureter. The aetiology remains unclear [1109-1111]. A single-system ureterocele is associated with a kidney with one ureter, and in duplex systems, the ureterocele belongs to the upper pole.

Ureteroceles usually cause obstruction of the upper pole, but the degree of obstruction and functional impairment is variable according to the type of ureterocele and upper pole dysplasia. In the orthotopic form, there is often no or only mild obstruction, and frequently the function of the moiety is normal or slightly impaired, and the corresponding ureter may be dilated. Cystic renal dysplasia is also associated with a single system ureterocele [1112]. Vesicoureteral reflux can be observed in 50% on the ipsilateral side and 20% on the contralateral side. Reflux into the ureterocele is uncommon [1113]. In the ectopic form, the upper pole is altered, frequently dysplastic, and hypo-functional or non-functional [1114]. The corresponding ureter is a mega-ureter. In the caeco-ureterocele (see definition below), the upper pole of the renal duplication is dysplastic and non-functional. Histological evaluation demonstrated that the changes represent a process of maldevelopment and may not result from infections or obstruction [1114].

3.16.2.1.1 Ectopic (extravesical) ureterocele

If any portion of the ureterocele extends into the bladder neck or urethra, it is called an ectopic ureterocele. Ectopic ureterocele is the most common form of ureterocele (> 80%). It can be voluminous, dissociating the trigone and slipping into the urethra, and may prolapse through the urethral meatus (caeco-ureterocele). The ureterocele orifice is tight, and located in the bladder itself or below the neck. The ureter corresponding to the lower pole moiety is raised by the ureterocele and is frequently refluxing or compressed by the ureterocele, leading to an obstructive mega-ureter. A contralateral renal duplication is associated with 50% of cases. Occasionally, large ureteroceles are responsible for reflux or obstruction of the contralateral upper tract.

3.16.2.1.2 Orthotopic (intravesical) ureterocele

The intravesical or orthotopic ureterocele is completely located in the bladder. Intravesical ureteroceles are mostly combined with a single kidney system and account for about 15% of cases. It is diagnosed more in older children or adults.

3.16.2.2 Ectopic ureter

The term ectopic ureter describes a ureter with the orifice located at the bladder neck, in the urethra or outside the urinary tract. The ureter can drain the upper pole of a duplex or single system. There is a fundamental difference between the sexes. In boys, the ectopic orifice is never below the external sphincter.

In girls, the ureteral orifice may be located [1115]:

- in the urethra, from the bladder neck to the meatus (35%);
- in the vaginal vestibule (34%);
- in the vagina (25%);
- in the uterus and Fallopian tube (6%).

In boys, the ureteral orifice may be located [1115]:

- in the posterior urethra (47%);
- in the prostatic utricle (10%);
- in the seminal vesicles (33%);
- in the vas deferens or ejaculatory ducts (10%).

*3.16.3 **Diagnostic evaluation***

3.16.3.1 Ureterocele

Prenatal US easily reveals voluminous obstructive ureteroceles [1116]. In cases with a small upper pole or a slightly obstructive ureterocele, prenatal diagnosis is difficult.

If prenatal diagnosis is impossible, the following clinical symptoms, besides incidental findings, can reveal the congenital anomaly at birth or later:

- At birth, a prolapsed and sometimes strangulated ureterocele may be observed in front of the urethral orifice. In a newborn boy, it might cause acute urinary retention, simulating urethral valves.
- The early symptom of pyelonephritis in either sex may lead to the diagnosis.
- Later symptoms can include dysuria, recurrent cystitis and urgency.

In cases of prenatal diagnosis, at birth US confirms the ureteral dilatation that ends at the upper pole of a renal duplication. It also demonstrates the presence of a ureterocele in the bladder, with a dilated ureter behind the bladder.

At this point, it is important to assess the function of the upper pole using nuclear renography of the region of interest. This is best assessed with DMSA, however this requires a careful systematic review of the images [1117]. Magnetic resonance urography may visualise the morphological status of the upper pole and lower moieties and of the contralateral kidney as well as it can detect renal scars [1118, 1119]. Using functional MR urography, differential renal function can be assessed with low intra- and interobserver variability [1120]. Based on the prevalence of high-grade reflux, VCUG is mandatory for identifying ipsilateral or contralateral reflux and assessing the degree of intra-urethral prolapse of the ureterocele [1121]. Urethrocystoscopy may reveal the pathology in cases where it is difficult to make the differential diagnosis between ureterocele and ectopic mega-ureter.

3.16.3.2 Ectopic ureter

Most of the ectopic mega-ureters are diagnosed primarily by US. In some cases, clinical symptoms can lead to diagnosis:

- In neonates: dribbling of urine, pyuria, and acute pyelonephritis.
- In young girls: permanent urinary incontinence besides normal voiding, or significant vaginal discharge as the equivalent of incontinence; an ectopic orifice may be found in the meatal region [1122].
- In pre-adolescent boys: epididymitis is the usual clinical presentation and the seminal vesicle may be palpable.

Ultrasound, radionuclide studies (DMSA, VCUG, MR urography, high-resolution MRI, and cystoscopy) are the diagnostic tools to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction [1123]. In some cases, the large ectopic ureter presses against the bladder and can look like a pseudo-ureterocele [1124].

Girls who present with life-long minimal urinary incontinence, never being dry, normal bladder function, complete emptying, and normal US are very suspicious for ectopic ureter. This needs to be excluded or confirmed by MRI as it is the most sensitive method [1125].

*3.16.4 **Management***

3.16.4.1 Ureterocele

Management is controversial with a choice between a non-operative approach, endoscopic decompression, ureteral re-implantation, partial nephroureterectomy, or complete primary reconstruction [1126-1131]. The choice of a therapeutic modality depends on the following criteria: clinical status of the patient (e.g. urosepsis); patient age; function of the upper pole; presence of reflux or obstruction of the ipsilateral or contralateral ureter; presence of bladder neck obstruction caused by ureterocele; intravesical or ectopic ureterocele; and caregivers' and the surgeon's preferences [1131]. When the diagnosis is made by US, prophylactic antibiotic treatment maybe indicated until a VCUG is performed.

3.16.4.1.1 Early treatment

In the presence of febrile infection or obstruction at the bladder neck, immediate endoscopic incision or puncture of the ureterocele is recommended. In a clinically asymptomatic child with a ureterocele and a non

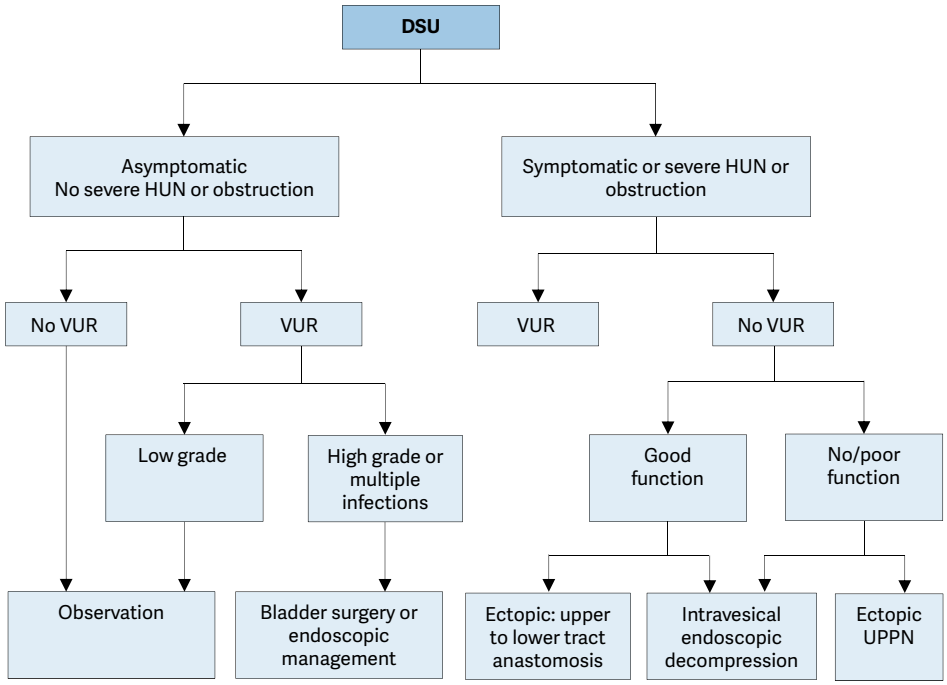
or hypofunctional upper pole, without significant obstruction of the lower pole and without bladder outlet obstruction, prophylactic antibiotic treatment is given until follow-up procedures are instigated. Decompression of the dilated system facilitates later reconstructive surgery [1132, 1133].

3.16.4.1.2 Re-evaluation

Active surveillance is an option for antenatally detected ureteroceles, but long-term follow-up is necessary [1134]. Conservative treatment may be adopted in asymptomatic patients without any bladder outlet obstruction, severe hydroureteronephrosis of the ureterocele moiety or high-grade (over grade III) reflux [1131, 1135]. A meta-analysis showed that, after primary ureterocele-incision, the re-operation rate is higher in those with an ectopic ureterocele compared to those with an intravesical ureterocele [1127]. Secondary surgery is necessary if decompression is not effective, significant reflux is present, or there is obstruction of the ipsi- or contralateral ureters, and/or bladder neck obstruction or retained ureterocele [1136].

Surgery may vary from upper pole nephrectomy to complete unilateral LUT reconstruction [1130, 1137-1139]. In an ectopic ureterocele with severe hydroureteronephrosis and without reflux, the primary upper tract approach without endoscopic decompression (partial upper-pole nephroureterectomy, pyelo/ureteropyelo/ureterostomy and upper-pole ureterectomy) has an 80% chance of being the definitive treatment [1131, 1140]. Also a LUT approach in those with a poorly or non-functioning upper pole is an option [1141]. Today, despite successful surgery, some authors think, that surgery may not be necessary at all in some patients [1142], as less aggressive surgical treatment and non-operative management over time can achieve the same functional results [1143]. There is emerging evidence on Minimally Invasive surgical approach (laparoscopic and robot assisted) for upper pole nephrectomy with similar operating time to open surgery [1144, 1145].

Figure 11: Algorithm for the management of duplex system ureteroceles after the first 3-6 months of life [1028]



DSU = duplex system ureterocele; HUN = hydroureteronephrosis; UPPN = upper pole partial nephrectomy; VUR = vesicoureteric reflux to the lower pole.

Obstruction is considered to be the presence of non-refluxing dilatation of non-ureterocele-bearing moieties (especially of the lower pole) or of an obstructive drainage pattern on diuretic renography.

3.16.4.2 Ectopic ureter

In the majority of cases, the upper pole is dysplastic and poorly functioning. There are a variety of therapeutic options, each with its advantages and disadvantages. In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definite solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ureteropyelostomy and upper-pole ureterectomy) are other therapeutic options especially in cases in which the upper pole has function worth preserving. These procedures can be performed through an open laparoscopic or robotic assisted approach [1145-1148]. So far there is no superior approach [1149]. In patients with bilateral single ectopic ureters (a very rare condition), an individual approach depending on the

sex and renal and bladder function of the patient is necessary. Usually the bladder neck is insufficient in these patients [1150].

3.16.5 Summary of evidence and recommendations for the management of obstructive pathology of renal duplication: ureterocele and ectopic ureter

Summary of evidence	LE
Ureterocele and ectopic ureter are associated with complete renal duplication, but they also occur in a single system.	1
In most cases, in young children (first years of life) diagnosis is done by US.	1
In older children clinical symptoms will prompt assessment.	1
Management includes a conservative approach, endoscopic decompression, partial nephroureterectomy, or complete primary reconstruction. Choice of treatment will depend on: • clinical status of the patient (e.g., urosepsis); • patient age; • function of the upper pole; • presence of reflux or obstruction of the ipsilateral or contralateral ureter; • presence of bladder neck obstruction caused by ureterocele; • intravesical or ectopic ureterocele.	3

Recommendations			LE	Strength rating
Ureterocele	Diagnosis	Use ultrasound (US), radionuclide studies (mercaptoacetyltriglycine (MAG3)/dimercaptosuccinic acid (DMSA)), voiding cystourethrography (VCUG), magnetic resonance urography, high-resolution magnetic resonance imaging (MRI), and cystoscopy to assess function, to detect reflux and rule out ipsilateral compression of the lower pole and urethral obstruction.	3	Weak
	Treatment	Select treatment based on symptoms, function and reflux as well on surgical and parenteral choices: observation, endoscopic decompression, ureteral re-implantation, partial nephroureteretomy, complete primary reconstruction. Offer, early endoscopic decompression to patients with an obstructing ureterocele.	3	Weak
Ectopic ureter	Diagnosis	Use US, DMSA scan, VCUG or MRI for a definitive diagnosis.	3	Weak
	Treatment	Treatment In non-functioning moieties with recurrent infections, heminephro-ureterectomy is a definitive solution. Ureteral reconstruction (ureteral re-implantation/ureteroureterostomy/ ureteropyelostomy and upper pole ureterectomy) are other therapeutic option especially in cases in which the upper pole has function worth preserving.	3	Weak

3.17 Disorders of sex development

3.17.1 Introduction

The formerly called ‘intersex disorders’ were the subject of a consensus document in which it was decided that the term ‘intersex’ should be changed to ‘disorders of sex development’ (DSD) [1151].

The new classification has arisen due to advances in knowledge of the molecular genetic causes of abnormal sexual development, controversies inherent to clinical management and ethical issues. Controversial and negative terminology, e.g. ‘pseudohermaphroditism’ and ‘hermaphroditism’, have been renamed according to the new pathophysiological insights. Furthermore, some conditions presenting with severe male genital malformation, such as penile agenesis and cloacal exstrophy, which could not be categorised, have also been included. The term ‘disorders of sex development’ is proposed to indicate congenital conditions with atypical development of chromosomal, gonadal or anatomical sex.

In addition, in 2017, the Parliamentary Assembly of the Council of Europe decided on a resolution called: "Promoting the human rights of and eliminating discrimination against intersex people" [1152]. The Parliamentary Assembly concluded that the majority of intersex people are physically healthy and only a few suffer from medical conditions that put their health at risk. Furthermore, they state that the prevailing medical view has been that intersex children's bodies can and should be made to conform to either a male or a female paradigm, often through surgical and/or hormonal intervention and that this should be done as early as possible and that the children should then be raised in the gender corresponding to the sex assigned to their body. The Parliamentary Assembly considers that this approach involves serious breaches of physical integrity, in many cases concerning very young children or infants who are unable to give consent and whose gender identity is unknown.

Therefore the Parliamentary Assembly called on Council of Europe member states with regard to effectively protecting children's right to physical integrity and bodily autonomy and to empowering intersex people as regards the following rights: medically unnecessary sex-"normalising" surgery, sterilisation and other treatments practised on intersex children without their informed consent should be prohibited and in addition that it has to be ensured that, except in cases where the life of the child is at immediate risk, any treatment that seeks to alter the sex characteristics of the child, including their gonads, genitals or internal sex organs, is deferred until such time as the child is able to participate in the decision, based on the right to self-determination and on the principle of free and informed consent.

The Panel refers to the consensus documents mentioned above as well as on the Parliamentary Assembly resolution. This chapter will focus on what is relevant for the practising paediatric urologist as the urologist is likely to be involved in neonates with DSD conditions.

Overall, evidence-based literature on DSD is sparse. There are no RCTs and most studies are based on retrospective clinical descriptive studies or on expert opinion. An exception is the risk of gonadal cancer, for which the level of evidence is higher [1153].

Disorders of sex development can present as prenatal diagnosis, neonatal diagnosis and late diagnosis. Prenatal diagnosis can be based on karyotype or US findings; neonatal diagnosis is based on genital ambiguity and late diagnosis is made on early or delayed puberty. In this guideline, focus is on the neonatal presentation where the paediatric urologist plays a major role. For late diagnosis we refer to endocrinology and gynaecology guidelines on precocious and delayed puberty where paediatric urologists play a minor role [1154, 1155].

Dealing with neonates with DSD requires a multidisciplinary approach, which should include geneticists, neonatologists, paediatric and adult endocrinologists, gynaecologists, psychologists, ethicists and social workers. Each team member should be specialised in DSD and a team should have treated enough patients to ensure experience.

*3.17.2 **Current classification of DSD conditions***

Since the International Consensus Conference on intersex and its subsequent publications on classification of the various conditions of DSD, several updates have been published with the latest published by the Global DSD Update Consortium in 2016 [1156]. As the field of DSD is continuously developing and knowledge and viewpoints change over time, an effort was made to include representatives from a broad perspective including support and advocacy groups with the goal to focus patient care upon the best possible QoL.

According to the international consensus in 2005, DSDs were defined as congenital conditions within which the development of chromosomal, gonadal and anatomic sex is atypical. The changes that were made according to terminology are as follows:

46XX DSD group formerly called female pseudohermaphrodite, over-virilisation of an XX female, and masculinisation of an XX female. In this group the vast majority is due to classic congenital adrenal hyperplasia (CAH) with various degrees of masculinisation. Among all DSD conditions together, 46XX CAH patients comprise approximately 80%. These conditions are extremely important since they can be potentially life threatening after birth because of salt loss phenomenon and immediate medical care is mandatory.

46XY DSD group in the past named male pseudohermaphrodite, undervirilisation of an XY male, and undermasculinisation of an XY male. This group is often quite heterogenous and includes the partial androgen insensitivity syndrome (PAIS) as well as the complete androgen insensitivity syndrome (CAIS) formerly called testicular feminisation.

Sex chromosome mosaicism DSD group (45X, 45X/46XY, 47XXY) consists of multiple variants with the mixed gonadal dysgenesis being the most important one. Many have a normal male phenotype and others asymmetric genitalia. One scrotal half often contains a gonad which is likely to be a testis whereas the other side is more a labia majora with usually no palpable gonad, most likely to be a streak gonad.

Ovotesticular DSD group was in the past called true hermaphrodite because of the presence of ovarian and testicular tissue in the same individual meaning that both – female and male structures – live together. There is great variability in phenotype with uni- or bilateral undescended gonads which can present as one ovary and one testis or as one or two ovotestes.

Non-hormonal/non-chromosomal DSD group was introduced as well, including newborns with cloacal exstrophy where bladder and intestines are exposed, patients with aphallia, and severe micropenis. The latter one is a normally formed penis with a stretched length of < 2.5 standard deviation below the mean [1151, 1157].

Micropenis should be distinguished from buried and webbed penis, which are usually of normal size. The length of the penis is measured on the dorsal aspect, while stretching the penis, from the pubic symphysis to the tip of the glans [1151].

*3.17.3 **Diagnostic evaluation***

3.17.3.1 The neonatal emergency

The first step is to recognise the possibility of DSD (Table 5) and to refer the newborn baby immediately to a tertiary paediatric centre, fully equipped with neonatal, genetics, endocrinology and paediatric urology units. Diagnosis of a 46XX DSD due to congenital adrenal hyperplasia should not be delayed and represents a neonatal emergency situation since the possibility of salt loss phenomenon can be fatal.

Table 5: Findings in a newborn suggesting the possibility of DSD
(adapted from the American Academy of Pediatrics)

Apparent male
Severe hypospadias associated with bifid scrotum
Undescended testis/testes with hypospadias
Bilateral non-palpable testes in a full-term apparently male infant
Apparent female
Clitoral hypertrophy of any degree, non-palpable gonads
Vulva with single opening
Indeterminate
Ambiguous genitalia

3.17.3.2 Family history and clinical examination

A careful family history must be taken followed by a thorough clinical examination including various laboratory tests and imaging modalities (Table 6).

Table 6: Diagnostic work-up of neonates with disorders of sex development

History (family, maternal, neonatal)
Parental consanguinity
Previous DSD or genital anomalies
Previous neonatal deaths
Primary amenorrhoea or infertility in other family members
Maternal exposure to androgens
Failure to thrive, vomiting, diarrhoea of the neonate
Physical examination
Pigmentation of genital and areolar area
Hypospadias or urogenital sinus
Size of phallus
Palpable and/or symmetrical gonads
Blood pressure

Investigations
Blood analysis: 17-hydroxyprogesterone, electrolytes, LH, FSH, TST, cortisol, ACTH
Urine: adrenal steroids
Karyotype
Ultrasound
Genitogram
hCG stimulation test to confirm presence of testicular tissue
Androgen-binding studies
Endoscopy

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinising hormone; TST = testosterone.

AA thorough clinical examination in a neonate presenting with ambiguous genitalia is important. As well as an accurate description of the ambiguous genitalia, detailed information should be given on palpability and localisation of the gonads. Information gathered by the various examinations described below should help the team to come to a final diagnosis. Medical photography can be useful but requires sensitivity and consent [1158].

Palpable gonad: If it is possible to feel a gonad, it is most likely to be a testis; this clinical finding therefore virtually excludes 46XX DSD.

Phallus: The phallus should be measured. A cotton bud placed at the suprapubic base of the implant of the stretched phallus allows for a good measurement of phallic length.

Urogenital sinus opening: The opening of the urogenital sinus must be well evaluated. A single opening has to be identified as well as a hymenal ring. Attention needs to be paid to the fusion of the labioscrotal folds as well as whether they show rugae or some discolouration.

Ultrasound can help to describe the palpated gonads or to detect non-palpable gonads. However, the sensitivity and specificity are not high. Mülllerian structures like the vagina or utricular structures can be evaluated as well [1159, 1160].

Genitography can provide some more information on the urogenital sinus, especially on the exact position of the confluence. Moreover, it gives evidence of possible duplication of the vagina.

Invasive diagnostics under general anaesthesia can be helpful in some cases.
On cystoscopy, the urogenital sinus can be evaluated as well as the level of confluence. It allows also for evaluation of the vagina or utriculus, the possible presence of a cervix at the top of the vagina.

Laparoscopy is necessary to obtain a final diagnosis on the presence of impalpable gonads and on the presence of Müllerian structures. If indicated, a gonadal biopsy can be performed [1161, 1162].

These investigations will help to distinguish the various conditions of DSD and provide quick evidence of congenital adrenal hyperplasia (CAH), which is the most frequently occurring DSD and the one that can become life-threatening within the first days of life because of salt loss phenomenon.

3.17.4 ***Gender assignment***

Nowadays it is obvious and clear that open and complete communications with caregivers and eventually the affected person are mandatory. Education and psychological support regarding the impact are needed for each individual to make sense of the condition, relate to their community and establish relationships. The lack of outcome data and different preferences make it extremely difficult to determine whether and when to pursue gonadal or genital surgery. Shared decision making is necessary, combining expert healthcare knowledge and the right of a patient or surrogate to make fully informed decisions. This entails a process of education, sharing of risks/benefits, articulating the uncertainties in DSD care and outcomes and providing time for the patient and family to articulate back the risks and benefits of each option. The goal of all involved should be to individualise and prioritise each patient.

However, adverse outcomes have led to recommendations to delay unnecessary surgery to an age when the patient can give informed consent. Surgery that alters appearance is not urgent. Recently the Parliamentary Assembly of the Council of Europe, the European Society for Paediatric Urology (ESPU) as well as the Societies

for Pediatric Urology have taken a position in the debate on surgery for DSD [1152, 1163, 1164]. In an open letter to the Council of Europe, the European Society for Paediatric Urology expressed its attitude to the abovementioned resolution and concentrated on a worrying issue dealing with medicosurgical care for children with DSD. It states that surgical interventions in children with DSD only being applied in emergency conditions is discordant with the definition of health according to the WHO, stating that health is not merely the absence of disease, but is a much broader concept, including physical, mental, and social domains. This especially applies to children, as favourable physical, social and emotional conditions are all critical factors for their optimal growth and development, which enables them to reach their full potential at adult age. As social and emotional interactions with the parents or caregivers, being the most important adults in a young child's life, form the basis for their future, treatment of children with DSD can best be organised in a patient- and family-centred multidisciplinary setting, in an atmosphere based on openness, commitment and trust. Physicians, who daily take care of children with a variety of congenital conditions, the same as their parents or caregivers, are committed to the current as well as the future health and well-being of all children entrusted to their care. In contrast to what is alleged in the recommendation, parents and caregivers implicitly act in the best interest of their children and should be respected as their outstanding representatives, and should not be put aside by claiming prohibition regulations regarding the well-informed decisions they make on their behalf. Finally in that open letter the ESPU advocate keeping the dialogue open with the professionals active in specialised centres for multidisciplinary, patient- and familycentred care as well as with patient societies, for which the present resolution is recognised as being a solid starting base [1165].

*3.17.5 **Risk of tumour development***

Individuals with DSD have an increased risk of developing cancers of the germ cell lineage, malignant germ cell tumours or germ cell cancer in comparison with to the general population [1166].

It is well-recognised that the highest risk prevalence (30-50%) is seen in conditions characterised by disturbed gonadal development such as incomplete testis development combined with a full block of embryonic germ cell maturation in patients with 46XY gonadal dysgenesis and in some patients with 45X/46XY DSDs. Conversely, patients with testosterone biosynthesis disorders and androgen action disturbances show a much lower risk (1-15%) for carcinoma *in situ* (CIS) development during childhood and a limited tendency towards invasive progression of the lesions [1167]. With regard to clinical management a gonadal biopsy at the time of a possible orchidopexy can be obtained for an initial assessment including regular self-exams and annual ultrasound [1153].

*3.17.6 **Recommendations for the management of disorders of sex development***

Recommendations	Strength rating
Newborns with DSD conditions warrant a multidisciplinary team approach.	Strong
Refer children to experienced centres where neonatology, paediatric endocrinology, paediatric urology, child psychology and transition to adult care are guaranteed.	Strong
Do not delay diagnosis and treatment of any neonate presenting with ambiguous genitalia since salt-loss in a 46XX CAH girl can be fatal.	Strong

3.18 Congenital lower urinary tract obstruction (CLUTO)

Introduction

The term congenital lower urinary tract obstruction (CLUTO) is used for a foetus, which during intrauterine US screening shows a dilatation of the upper and lower urinary tract. During pregnancy the diagnosis is usually based only on US examinations. There is a broad spectrum of conditions, that could cause an intrauterine dilatation of the urinary tract. Post-partum diagnosis comprises any anatomical and functional disorder/anomaly/malformation causing a dilatation e.g. posterior/anterior urethral valve, urethral atresia/dysplasia/stenosis prune belly syndrome, dilating reflux. Cloacal malformation, ureterocele, a Megacystis-Microcolonintestinal hypoperistalsis or Megacystis-Megaureter Syndrome [1168-1171].

Megacystis

In the first trimester, foetal megacystis is defined as a bladder with a longitudinal diameter ≥ 7 mm, and in the 2nd and 3rd trimester as an enlarged bladder failing to empty during an extended US examination lasting at least 40 minutes. Two thirds of cases are secondary to CLUTO and the remainder are associated with genetic syndromes, developmental or chromosomal abnormalities including anorectal malformations; 14% were normal or having isolated urological abnormality (e.g. VUR, Duplex system) [1172]. A more recent systematic review showed that at least 45% of cases have oligohydramnios and 15% have chromosomal abnormalities, most of them being trisomy

13, 18 and 21. Final diagnoses were posterior urethral valve (PUV) (57%), urethral atresia/stenosis (7%), prune-belly syndrome (4%), megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) (1%), cloacal abnormality (0.7%) and undefined pathologies (36.5%). Termination of pregnancy rate was 50% [1173].

The prognosis of the foetus depends on the underlying pathology, the timing of diagnosis, presence of an oligo-, anhydramnios and bladder volume. Fontanella *et al* developed a staging system of CLUTO. They described three groups: severe (Bladder volume ≥ 5.4 cm^3 and/or oligo-, an hydramnios before 20 weeks), moderate (Bladder volume < 5.4 cm^3 and/or normal amniotic fluid at 20 weeks) and mild (Normal AF at 26 weeks) [1174]. This staging system can be used to predict perinatal mortality and post-natal estimated GFR. Another recent systematic review on prognosis of megacystis patients revealed an overall intrauterine spontaneous resolution of 32%, with better resolution rates in early (before 18 weeks) megacystis cases (40% vs. 12%) [1175].

3.18.1 ***Posterior urethral valves***

3.18.1.1 Epidemiology, aetiology and pathophysiology

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period. A recent systematic review showed, that the risk for chronic kidney disease (CKD) could be up to 32% and for end-stage kidney disease (ESKD) up to 20% [1176]. Up to 17% of paediatric ESKD can be attributed to PUV [1177]. An incidence of PUV of 1 in 7,000-8,000 live-births has been estimated [1169, 1178].

3.18.2 ***Classification systems***

3.18.2.1 Urethral valve

Up until today, the original classification by Hugh Hampton Young is the most commonly used classification [1179]. Hugh Hampton Young described three categories: type I, type II and type III. However, today, only type I and type III are found to be obstructive. As type II seems to be more like a fold and not obstructive, it is no longer referred to as a valve. Hampton Young's descriptions of type I and III are as follows:

Type I (90-95%). 'In the most common type there is a ridge lying on the floor of the urethra, continuous with the verumontanum, which takes an anterior course and divides into two fork-like processes in the region of the bulbomembranous junction. These processes are continued as thin membranous sheets, direct upward and forward which may be attached to the urethra throughout its entire circumference. It is generally supposed that the valves have complete fusion anteriorly, leaving only an open channel at the posterior urethral wall. Yet, the fusion of the valves anteriorly may not be complete in all cases, and at this point a slight separation of the folds exists' [1179].

Type III. 'There is a third type which has been found at different levels of the posterior urethra and which apparently bears no such relation to the verumontanum. This obstruction was attached to the entire circumference of the urethra, with a small opening in the centre [1169]. The transverse membrane described has been attributed to incomplete dissolution from the urogenital portion of the cloacal membrane [1180]. The embryology of the urethral valves is poorly understood. The membrane may be an abnormal insertion of the mesonephric ducts into the foetal cloaca [1181].

3.18.3 ***Diagnostic evaluation***

An obstruction above the level of the urethra affects the whole urinary tract to varying degrees.

- The prostatic urethra is distended and the ejaculatory ducts may be dilated due to urinary reflux.
- The bladder neck is hypertrophied and rigid.
- The hypertrophied bladder occasionally has multiple diverticula.
- Nearly all valve patients have dilatation of both upper urinary tracts. This may be due to the valve itself and the high pressure in the bladder, or due to obstruction of the ureterovesical junction by the hypertrophied bladder.
- If there is secondary reflux, the affected kidney functions poorly in most cases.

During prenatal US screening, bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a urethral valve. A thick-walled bladder seems to be of better prediction of a PUV than a dilated posterior urethra ('keyhole' sign) [1182]. However, differentiation between obstructive and non-obstructive aetiologies on prenatal US is challenging as both have a similar US appearance [1183] In the presence of increased echogenicity of the kidney, dilatation of the urinary tract and oligohydramnion, the diagnosis of a PUV should strongly be considered. Prenatal US is adequate in most of the cases (90%) [1184]. However in some circumstances when technical US conditions are poor such as oligo- or anhydramnios, large maternal body habitus, unfavourable position of the foetus or in suspicion of complex foetal anomalies such as accompanying gastrointestinal system, foetal MRI may provide additional information [1184-1186].

Post-natally, a voiding cystourethrogram confirms the diagnosis of a PUV. This study is essential whenever there is a question of an infravesical obstruction, as the urethral anatomy is well-outlined during voiding. A secondary reflux is observed in at least 50% of patients with PUV [1187]. Reflux is consistently associated with renal dysplasia in patients with PUV. It is generally accepted that reflux in the renal units acts as a 'pressure pop-off valve', which would protect the other kidney, leading to a better prognosis [1188]. Other types of pop-off mechanisms include bladder diverticula and urinary extravasation, with or without urinary ascites [1189]. However, in the long-term, this supposed protective effect did not show a significant difference compared to other patients with PUV [1190, 1191].

Nuclear renography with split renal function is important to assess kidney function (DMSA or MAG3). Creatinine, blood urea nitrogen and electrolytes should be monitored closely during the first few days. Initial management includes a multi-disciplinary team involving a paediatric nephrologist. The clinician must be aware of a noteworthy association between PUV and undescended testes and/or inguinal hernia [1192]. Undescended testes occurred in 12-17% of PUV which is consistent with a 10-fold increase [1193].

*3.18.4 **Management***

3.18.4.1 Antenatal treatment

Today most of PUV are discovered before birth [1168-1171]. The intrauterine obstruction leads to a decreased urine output, which could result in an oligo- or anhydramnios. Amniotic fluid is necessary for normal development of the lung and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem.

Kidneys start to produce urine at around 10th weeks of antenatal life. Many of the megacystis cases (7-15 mm) with normal karyotype spontaneously resolve before 20 weeks, whereas it is unlikely in those with a bladder length > 15mm (> 12mm before age of 18 Weeks of gestation) [1183, 1194, 1195]. Antenatal imaging of kidneys before 20 weeks is difficult and in rare instances imaging could be done earlier via transvaginal route [1196]. The possible spontaneous resolution chance of bladder enlargement and timing of proper kidney imaging are possibly the main obstacles on the optimum timing for prenatal intervention.

As renal dysplasia is not reversible, it is important to identify those foetuses with good renal function. A sodium level below 100 mmol/L, a chloride value of < 90 mmol/L and an osmolarity below 200 mOsm/L found in three foetal urine samples gained on three different days are associated with a better prognosis [1197]. Urine samples before 23 weeks of gestation (ß2-microglobline, sodium, chloride and calcium) may be helpful to distinguish between those who could benefit from intrauterine therapy and those in whom the outcome is most likely to be compromised [1198]. The status of amniotic fluid, the appearance of the kidneys as well as the foetal urine biochemistry could be helpful in counselling the caregivers.

Prenatal interventions aim to restore amniotic fluid volume and attenuate the risk of pulmonary hypoplasia or further renal damage [1199]. Decision for prenatal intervention can be based on a staging system that is composed of renal ultrasonographic findings, amnion amount and foetal urine biochemistry [1170]. Early intervention – before the age of 16 weeks of gestation, may be beneficial for the renal function, however making the correct diagnosis and the detection of other severe co-morbidties is extremly difficult at this time point [1200]. Later interventions are mostly of benefit for the lung development, but not for renal function.

The placing of a vesicoamniotic shunt has a complication rate of 21-59% with dislocation of the shunt being the most common one [1199]. The PLUTO-trail (randomised study) failed to show any long-term benefit on renal function by placing a visual analogue scale (VAS) [1201]. A recent meta-analysis on interventions for CLUTO reported that VAS resulted in a higher perinatal survival rate than conservative management (57.1% vs 38.8%) with no significant differences in 6-12 month survival, 2-year survival or postnatal renal function [1202]. Foetal cystoscopy with laser ablation has a high complication rate without evidence for the effectiveness of these interventions [1203]. To avoid the severe complication of the laser ablation, balloon dilation is tried [1204]. The number of patients included and designs of these studies are insufficient to give any recommendations. Parental information is very important and the natural history of CLUTO including the postnatal outcomes with or without prenatal treatment as well as the uncertainties and/or controversies about CLUTO diagnosis and treatment should be discussed [1199].

3.18.4.2 Postnatal treatment

Bladder drainage. If a boy is born with suspected PUV, drainage of the bladder and, if possible, an immediate VCUG is necessary. A neonate can be catheterised with a small catheter without a balloon, preferably a feeding tube. A VCUG is performed to see if the diagnosis is correct and whether the catheter is within the bladder and not in the posterior urethra. An alternative option is to place a suprapubic catheter, perform a VCUG and leave the tube until the neonate is stable enough to perform an endoscopic incision or resection of the valve.

Valve ablation. When the medical situation of the neonate has stabilised and the creatinine level decreased, the next step is to remove the intravesical obstruction. In cases where the urethra is too small to safely pass a small foetal cystoscope, a suprapubic diversion is performed until valve ablation can be performed. Small paediatric cystoscopes and resectoscopes are now available either to incise, ablate or to resect the valve at the 4-5, 7-8 or 12 o'clock position, or at all three positions, depending on the surgeon's preference. It is important to avoid extensive electrocoagulation, as the most common complication of this procedure is stricture formation. Two studies demonstrated a lower urethral stricture rate using the cold knife compared to diathermy [1205, 1206]. Within the three months following initial treatment, effectiveness of the treatment should be demonstrated either by clinical improvement (US and renal function), control VCUG or a re-look cystoscopy, depending on the clinical course [1207-1209].

Vesicostomy. If the child is too small and/or too ill to undergo endoscopic surgery, a suprapubic diversion is performed to drain the bladder temporarily. If initially a suprapubic tube has been inserted, this can be left in place for six to twelve weeks. Otherwise, a cutaneous vesicostomy provides an improvement or stabilisation of the UUT in up tp 90% of cases [1210, 1211]. Although there has been concern that a vesicostomy could decrease bladder compliance or capacity, so far there are no valid data to support these expectations [1212, 1213]. Moreover, it was shown in PUV patients with stage 3 CKD that adding vesicostomy to valve ablation no long-term benefit was noted from diversion in the ultimate incidence of ESKD [1214].

High diversion. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. The choice of urinary diversion depends on the surgeon's preference for high-loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy, with each technique having advantages and disadvantages [1215-1218]. Diversion can delay progression to end stage renal failure [1214]. Reconstructive surgery should be delayed until the UUT has improved as much as can be expected.

Reflux is very common in PUV patients (up to 72%) and it is described bilaterally in up to 32% [1219]. During the first months of life, antibiotic prophylaxis may be given especially in those with high-grade reflux [930] and in those with a phimosis, circumcision can be discussed in order to reduce the risk of UTIs [1220]. However, there are no randomised studies to support this for patients with PUV. Early administration of oxybutynin may improve bladder function as shown in one study with eighteen patients [1221]. High-grade reflux is associated with a poor functioning kidney and is considered a poor prognostic factor [1222, 1223]. However, early removal of the renal unit seems to be unnecessary, as long as it causes no problems. Moreover, in the long term it may be necessary to augment the bladder and in this case the ureter may be used [1224]. Deterioration of renal function without a fixed obstruction and higher urine output (polyuria) may lead to an overdistension of the bladder during the night. Drainage of the bladder during the night by a catheter may be beneficial for the hydronephrosis as well as for renal function [1225, 1226]. Patients with high daytime PVR urine may benefit from CIC [1227, 1228]. In those who do not want or are not able to perform a CIC via urethra, the placement of a Mitrofanoff is a good alternative [1229].

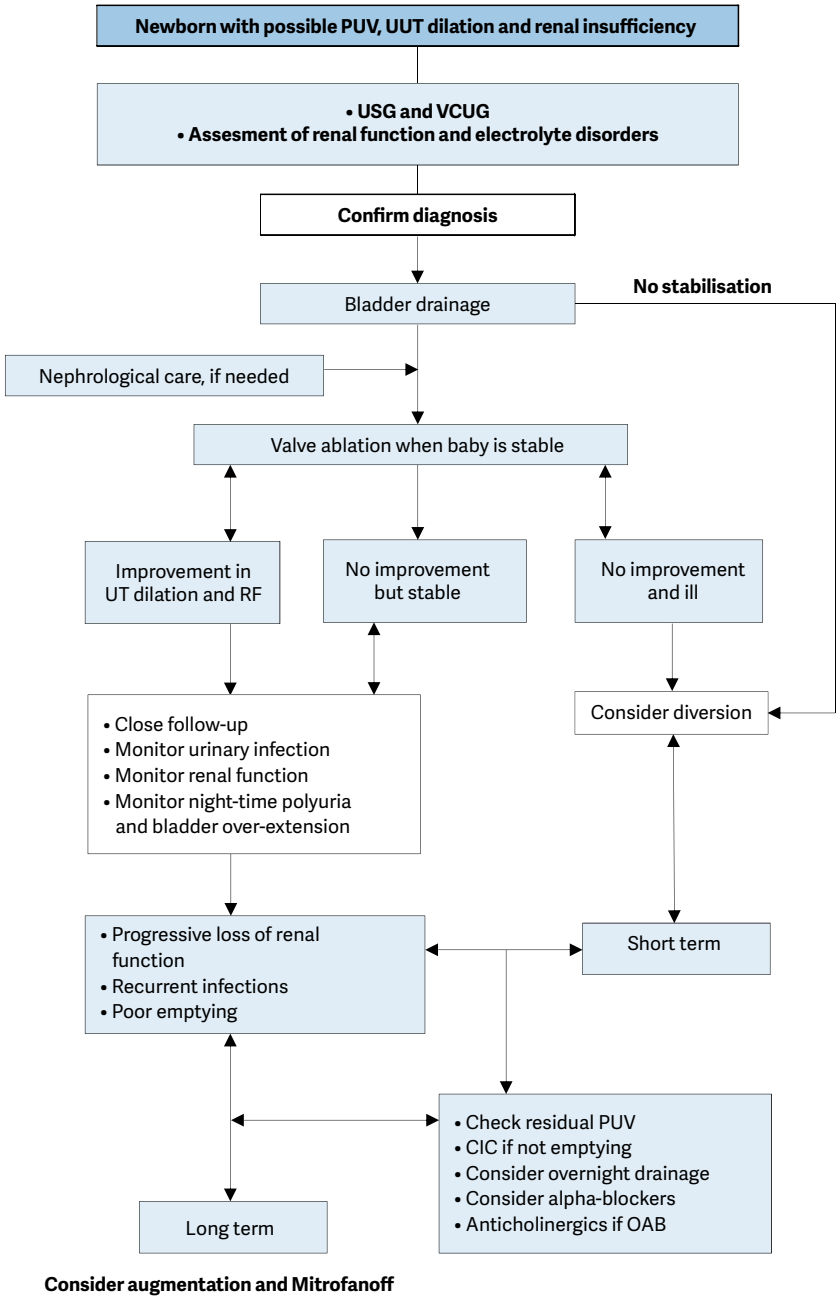
3.18.5 ***Follow-up***

Several prognostic factors have been described. Different serum nadir creatinine levels are given in the literature (0.85 mg/dl-1.2 mg/d (µmol/L) [1230-1233]. Renal parenchyma quantity (total renal parenchymal area) and quality (corticomedullary differentiation and renal echogenicity) on initial postnatal US also have prognostic value [1234].

Life-long monitoring of these patients is mandatory, as bladder dysfunction ('valve bladder') is not uncommon and the delay in day- and night-time continence is a major problem [1235, 1236]. The literature demonstrates that urodynamic studies plays an important role in the management of patients with valve bladder especially in those with suspicion of bladder dysfunction [1237, 1238]. Poor bladder sensation and compliance, detrusor instability and polyuria (especially at night) and their combination are responsible for bladder dysfunction. In those with bladder instability, anticholinergic therapy can improve bladder function. However, there is a low risk of reversible myogenic failure (3/37 patients in one study) [1239, 1240]. In patients with poor bladder emptying, α-blocker can be used to reduce the PVR urine, as demonstrated in one study with 42 patients using terazosin (mean PVR was reduced from 16 to 2 mL) [1241]; in another study tamsulosin was effective [1242]. Concerning bladder neck incision, there is no Panel consensus concerning indication and efficacy. High creatinine nadir (> 1 mg/dL) and severe bladder dysfunction are risk factors for renal replacement therapy [1243, 1244]. Renal transplantation in these patients can be performed safely and effectively [1245, 1246]. Deterioration of the graft function is mainly related to LUTD [1245]. Therefore, it is essential to have and keep a good reservoir function. An assessment and treatment algorithm is provided in Figure 12.

There are only few reports on sexual function and fertility in patients with PUV demonstrating some impairment especially in those who are on dialysis [1247, 1248]. In a review the majority have good erectile function (74- 94%) and a fertility comparable to the normal population [1249]. However, a negative influence of the individual patient's fertility has to be taken into account, as these patients have a higher risk for bilateral cryptorchidism, recurrent epididymitis and ESRD [1249].

Figure 12: An algorithm on the assessment, management and follow-up of newborns with possible PUV


Newborn with possible PUV, UUT dilation and renal insufficiency
• USG and VCUG
• Assesment of renal function and electrolyte disorders
Confirm diagnosis
Bladder drainage
No stabilisation
Nephrological care, if needed
Valve ablation when baby is stable
Improvement in UT dilation and RF
No improvement but stable
No improvement and ill
Consider diversion
• Close follow-up
• Monitor urinary infection
• Monitor renal function
• Monitor night-time polyuria and bladder over-extension
• Progressive loss of renal function
• Recurrent infections
• Poor emptying
Short term
• Check residual PUV
• CIC if not emptying
• Consider overnight drainage
• Consider alpha-blockers
• Anticholinergics if OAB
Long term
Consider augmentation and Mitrofanoff

CIC = clean intermittent catheterisation; OAB = overactive bladder; PUV = posterior urethral valve; RF = renal function; UT = urinary tract; UUT = upper urinary tract; VCUG = voiding cystourethrogram.

*3.18.6 **Summary***

Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period and despite optimal treatment result in renal insufficiency in nearly one-third of cases. Bilateral hydroureteronephrosis and a distended bladder are suspicious signs of a PUV in neonates. A VCUG confirms a PUV diagnosis. Nuclear renography with split renal function is important to assess kidney function and serum creatinine nadir above 80 µmol/L is correlated with a poor prognosis. Today, antenatal therapy is becoming more and more popular. Identification of those with an obstructive uropathy and definiton of those who would benefit from early antenatal intervention are the major challenges. Postnatal treatment

includes bladder drainage, either transurethral or suprapubic and if the child is stable enough, endoscopic incision of the valve is performed. If a child is too small and/or too ill to undergo endoscopic surgery, a vesicostomy is an option for bladder drainage. If bladder drainage is insufficient to drain the UUT, high urinary diversion should be considered.

In all patients life-long monitoring is mandatory, as bladder dysfunction is quite common and may cause progressive upper tract deterioration, if not managed properly. In the long-term between 10 and 47% of patients may develop end-stage renal failure. Renal transplantation in these patients can be performed safely and effectively.

- **Anterior urethral valve (AUV)**

Anterior urethral valve is a semilunar or iris-like band of tissue on ventral aspect of urethra. It can be isolated, in association with or confused with urethral diverticulum. The aetiology of isolated AUV is speculated to be secondary to congenital urethral obstruction, malunion of glanular and penile urethra, congenital cystic dilatation of peri-urethral glands or ruptured distal lip of a syringocele [1250]. Anterior urethral valve occurs less frequently than PUV. It can be present in the bulbous urethra, the penoscrotal junction and penile urethra. Patients may present with poor urinary stream, penile ballooning, UTI or haematuria. Anterior urethral valves have been classified by Firlit *et al.* depending on the presence of diverticulum and the dilatation of urethra and upper tract [1251]. The diagnosis is based on VCUG with possible findings of dilated or elongated posterior urethra, a dilatation of the anterior urethra, a thickened trabeculated bladder, a hypertrophied bladder neck, VUR, and urethral diverticula. In doubtful cases, retrograde urethrography may be helpful showing linear filling defect along the ventral wall, or it may show a dilated urethra ending in a smooth bulge or an abrupt change in the caliber of the dilated urethra on VCUG [1252]. Treatment is performed mainly by endoscopic valve ablation. In selected patients, a temporary diversion may be considered until the child is big enough for endoscopy to be possible. Open surgery is reserved in patients with very large diverticulum and defective spongiosum. Renal failure may develop in 22% and the risk is highest in patients with pre-treatment azotaemia, VUR and UTI [1253].

- **Anterior urethral diverticulum (AUD):**

Common postnatal presenting features of AUD are compressible ventral penile swelling, urinary dribble postmicturition, voiding difficulty, poor stream, and recurrent UTIs [1254-1256]. Diagnosis is made by VCUG with or without a retrograde urethrogram. In small AUD, endoscopic cutting or deroofing of distal lip of the diverticulum can be used as a treatment modality. Larger diverticulum requires excision of the diverticulum with a twolayered urethroplasty; or marsupialisation with staged urethroplasty. In cases of urosepsis and obstructive uropathy, a suprapubic catheter may be placed. Once the infant's condition improves, temporary urinary diversion with vesicostomy or proximal cutaneous urethrostomy can be performed before definitive surgical management [1257, 1258]. The diverticulum is associated with a distal lip-like tissue which may be confused with a valve. Anatomically, AUV have normal corpus spongiosum development whereas AUD have incomplete spongious tissue formation [1257].

- **Syringocele**

Cowper glands are two bulbourethral glands located within the urogenital diaphragm and secrete pre-ejaculatory mucus on both sides through the external sphincter into the urethra 1-2 cm distal to the sphincter. Syringocele is the cystic dilatation of these glands. The aetiology can be congenital (retention cyst of the intraurethral portion of the duct) or acquired (trauma or infection). It has been classified as simple, imperforate, perforate and ruptured [1259]. A simpler grouping is suggested to merge simple, perforate and ruptured into "open syringocele" and imperforate to "closed syringocele". Closed syringoceles cause obstructive symptoms and open ones act as a diverticula and cause post-voiding drippling and sometimes obstruction due to orientation of one membrane into urethra [1260]. However, it is better to simply categorise into two groups as obstructing and non-obstructing in terms of understanding pathophysiology and management [1261]. Depending on the syringocele type, patients present with post-void dribbling, urethral discharge, UTI, perineal pain, haematuria, obstructive voiding symptoms, dysuria and retention. Diagnosis is based on antegrade and/ or retrograde urethrogram which shows a cystic defect distal to prostate. If the VUC/RGU are inconclusive, US and/or MRI may be used if open reconstruction is being planned. Endoscopic deroofing of the cyst in both obstructing and non-obstructing syringoceles is an effective method of marsupialisation [1262]. In cases where endoscopic approach is not feasible open correction may be considered.

- **Cobb's collar**

Cobb's collar is a congenital membranous stricture of the bulbar urethra. It is different from congenital obstructive posterior urethral membrane (COPUM) and is independent of the verumontanum and external sphincter and may represent a persistence of part of the urogenital membrane [1263]. Voiding cystourethrogram shows narrowing in the proximal bulbar urethra with folds extending proximally, a dilated

posterior urethra, prominent bladder neck and other findings of infravesical obstruction. Treatment is an endoscopic incision; using cold-knife showed lower recurrence rates than electrocautery [1264].

- **Urethral atresia/hypoplasia**

Male urethral atresia is a congenital, complete obstruction of the urethra caused by a membrane that is usually located at the distal end of the prostatic urethra. The urethra distal to this point is usually hypoplastic, presumably from lack of foetal voiding [1265]. Urethral atresia is associated with bladder distention, VUR, hydronephrosis and renal dysplasia [1266]. Most cases reported have the phenotypic characteristics of the prune belly syndrome. Antenatal intervention may be beneficial in terms of foetal survival [1267]. Although progressive augmentation by dilating the urethra anterior (PADUA) procedure was described as a treatment modality, the majority of cases requires some form of supravesical diversion [1265, 1266].

- **Posterior Urethral Polyps:**

Although, posterior urethral polyps (PUP) does not cause antenatal hydronephrosis, it could cause obstruction later in life. Posterior Urethral Polyps is a polypoid, pedunculated, fibroepithelial lesion arising in posterior urethra proximal to the verumontanum. It lies on the floor of the urethra with its tip reaching into the bladder neck and obstruction occurs because of distal displacement of polyp during urination [1268]. Patients complain of dysuria, haematuria and obstructive symptoms such as poor urinary stream and intermittent retention episodes. Diagnosis can be suspected by VCUG and/or US but is confirmed during cystourethroscopy. Treatment is usually an endoscopic resection of the polyp. The course of the disease is benign and no recurrences were reported in the literature [1269, 1270].

*3.18.7 **Summary of evidence and recommendations for the management of posterior urethral valves***

Summary of evidence	**LE**
Posterior urethral valves are one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period.	1b
Antenatal therapy could be discussed based on ultrasound findings, fetal urine biochemistry amount of amnion fluid and chromosomal status.	4
Despite optimal treatment nearly one-third of the patients end up in renal insufficiency.	2b
Bilateral hydroureteronephrosis and a distended bladder are suspicious signs on US; a VCUG confirms the diagnosis.	2b
Serum creatinine nadir above 85 µmol/L is correlated with a poor prognosis.	2a
In the long-term up to 20% of patients develop end-stage renal failure due to primary dysplasia and/or further deterioration because of bladder dysfunction. Renal transplantation in these patients is safe and effective, if the bladder function is normalised.	2a

Recommendations	**LE**	**Strength rating**
Diagnose posterior urethral valves (PUV) initially by ultrasound but a voiding cystourethrogram (VCUG) is required to confirm the diagnosis.	3	Strong
Assess split renal function by dimercaptosuccinic acid scan or mercaptoacetyltriglycine (MAG3) clearance. Use serum creatinine as a prognostic marker.		Strong
Vesico-amniotic shunt antenatally is not recommended to improve renal outcome.	1b	Weak
Offer endoscopic valve ablation after bladder drainage and stabilisation of the child.	3	Strong
Offer suprapubic diversion for bladder drainage if the child is too small for valve ablation.		Strong
Offer a high urinary diversion if bladder drainage is insufficient to drain the upper urinary tract and the child remains unstable.		Strong
Monitor bladder and renal function life-long, in all patients.	3	Strong

3.19 Rare Conditions in Childhood

*3.19.1 **Urachal remnants***

3.19.1.1 Introduction

The urachus is an embryonic structure arising as a result of the separation of the allantois from the ventral cloaca. The allantois appears on day sixteen as a tiny, fingerlike outpouching from the caudal wall of the yolk sac, which is contiguous with the ventral cloaca at one end and the umbilicus at the other. The ventral portion of the cloaca develops into the bladder after cloacal division by the urogenital septum. Thus, the bladder

initially extends all the way to the umbilicus [1271]. With progressive foetal development, as the bladder descends into the pelvis, the attachment between the umbilicus and the urachus becomes looser and the apical portion progressively narrows to a small, epithelialised, fibromuscular strand by the fourth or fifth month of gestation. The urachus then obliterates completely by birth, forming the median umbilical ligament [1272-1274].

The urachus varies from 3 to 10 cm in length and from 8 to 10 mm in diameter. It is a three-layered tubular structure, the innermost layer being lined with transitional epithelium, the middle layer composed of connective tissue, and the outermost muscular layer in continuity with the detrusor muscle [1275].

Urachal remnants (URs) originate from failure of the obliteration of the allantois, resulting in a urachal anomaly such as (1) urachal sinus, (2) urachal cyst, (3) vesico-urachal diverticulum, and (4) patent urachus [1272, 1273, 1276]. Most often the urachal anomaly is asymptomatic, but it occasionally may become infected, may cause urinary symptoms, or develop a urachal carcinoma in later life [1275, 1277].

3.19.1.2 Epidemiology

Reports of occurrence rates in the literature vary broadly from a very rare disease in the older literature to a fairly common problem. Robert *et al.* found that URs were present in 61.7% of patients younger than 16 years [1278]. They also noted that the frequency of URs decreased with increasing age. This supports a physiological regression of URs with age. Stopak *et al.* attributed this upsurge to increased awareness among community paediatricians and improvements in US that made visualisation of urachal remnants easier [1279].

Clinical studies and paediatric autopsy studies in the past have shown a much lower incidence. Rubin found an incidence of 1 in 7,610 cases of patent urachus and 1 in 5,000 cases of urachal cysts [1280]. Nix *et al*. noted three anomalies out of 1,168,760 hospital admissions, and Blichert-Toft *et al.* reported five UR cases out of 40,000 patients [1281, 1282]. The incidence rate in males is a little higher than in females [1283, 1284].

The range of the various URs reported in the literature is 10% to 48% for patent urachus, 31% to 43% for urachal cyst, 18% to 43% for urachal sinus and 3% to 4% for urachal diverticulum [1285, 1286].

3.19.1.3 Symptoms

A patent urachus causes continuous or intermittent urine leakage from the umbilicus causing umbilical granulation and erythema in infants [1285]. A urachal cyst is usually diagnosed (1) incidentally, or (2) when it becomes infected causing abdominal pain and discharge of pus from the umbilicus or recurrent UTIs when it drains into the bladder.

The most common symptom is umbilical granulation, discharge and erythema in infants and abdominal pain in older children [1285].

Other symptoms of infected urachal anomalies can vary from high fever, abdominal pain, urinary tract infections, LUTS and/or an abdominal mass [1286-1290]. A urachal diverticulum is often asymptomatic and is usually found incidentally during investigations for other problems. An alternating sinus can empty either into the bladder or the umbilicus and this characteristic is responsible for various presentations [1291]. Infection has been reported as the most common complication in urachal anomalies [1292]. Severe infection may develop into peritonitis and sepsis. Cultures from umbilical discharge usually show *Staphylococcus, Streptococcus* and *E. Coli* [1293].

- **<u>Other congenital anomalies:</u>**

Ashley found a simultaneous anomaly in 17 of 46 children, of which VUR was the most common anomaly (6 patients) [1294]. Other investigators reported associated anomalies in cases of persistent URs including meatal stenosis, hypospadias, umbilical and inguinal hernias, cryptorchidism, anal atresia, omphalocele, ureteropelvic obstruction and most frequently, VUR [1284, 1295-1297].

3.19.1.4 Diagnosis

In the majority of cases with complaints of a UR, a careful history and physical examination will confirm the suspicion of a UR. In many patients this can be confirmed by US studies [1278]. An MRI or CT scan may be necessary in a minority of children [1289]. Because of the association with other congenital abnormalities, other studies such as a VCUG or cystoscopy may be undertaken as well. In general, the VCUG is only undertaken when the child also presents with UTI or when the US shows signs of upper tract abnormalities. For the diagnosis per se it is not necessary [1298]; however, a VCUG may be useful for defining the type of urachal anomaly and evaluating a population that may be at higher risk for VUR.

3.19.1.5 Treatment

If a UR is symptomatic, the standard approach has been surgical removal. In most cases it should be done as an elective procedure, following appropriate treatment of active inflammation, and infection is possible. Pre-operative IV-dosage of antibiotic like Cefazolin is generally sufficient. A Pfannenstiel, periumbilical or infraumbilical midline incision can all be used for the open surgical approach [1288, 1299]. Even in symptomatic infants a more conservative approach is possible as well, especially in children less than six months old. Observation and treatment with antibiotics if necessary and radiographic monitoring are a safe approach [1285, 1300, 1301]. Dethlefs *et al*. reported a 90% successful outcome [1287], while Naiditch *et al.* reported that 44 of 78 symptomatic patients resolved under observation [1290]. More recently the laparoscopic approach has been advocated, and shown to be safe [1301-1303]. Surgery is not without risk. The rate of complications following surgical removal varies from 0 to 20%: usually wound infections [1279, 1287-1290, 1299]. Considering the probable additional risk of anaesthesia in very young children any surgical procedure needs to be assessed carefully [1304, 1305].

3.19.1.6 Pathology of removed remnants

Removed specimens may show inflammation or a cystic structure [1287]. Patients presenting without symptoms are as likely to have epithelial elements in the UR as those presenting with symptoms [1289].

3.19.1.7 Urachal cancer

Urachal anomalies are thought to be associated with an increased risk of bladder adenocarcinoma in adults, and urachal adenocarcinoma has an estimated incidence of 0.18 per 100,000 individuals yearly [1306]. These cases account for 0.1 to 0.3% of all bladder malignancies and 20 to 39% of bladder adenocarcinomas [1307]. Urachal adenocarcinoma (UrC) is very rare, especially when one considers that up to 62% of children under 16 years of age may have a UR [1278, 1308]. A study by Copp *et al.* found no association between the presence of UR symptoms and the presence or absence of epithelial tissue in pathology specimens, leading them to conclude that UR symptoms have poor predictive value for malignancy potential in these remnants [1284].

Gleason *et al.* found that 5,721 URs would need to be excised to prevent a single case of urachaladenocarcinoma out of the nearly 65,000 patients reviewed [1306]. Assuming that epithelium is required in the development of urachal adenocarcinoma, the extrapolated Number Needed to Treat (NNT) would be more than 8,000, as nearly 30% of urachal anomalies are void of an epithelial component. Less than 5% of urachal cancers have a non-epithelial origin such as sarcoma [1309]. The presenting symptoms in adults are different from those in children: in a study of 130 adult patients, Ashley *et al.* found that 49% presented with haematuria and 27% with pain. In 51% a urachal carcinoma was diagnosed: adenocarcinoma, with 58% high grade cancer. In addition, 20% had metastases at diagnosis, the overall 5-year cancer specific survival rate in the UrC cohort was 49% [1310]. Stasis of urine and crystallisation promotors such as mucus or desquamated epithelium in the UR are most likely the cause for malignant degeneration as well as stone formation in the adult patient. At present no long-term follow-up on untreated UR in children is available and there is no evidence that urachal anomalies in children increase the likelihood of future malignancy [1285, 1311].

3.19.1.8 Conclusion

Urachal remnants appear to be more common than previously reported. During the first 6-12 months of life spontaneous resolution is common. Excision of symptomatic urachal anomalies is an effective and safe means of treatment, with minimal morbidity. However, most patients with simple and asymptomatic lesions do not appear to benefit from excision, as the risk of malignancy later in life is vanishingly remote. Early intervention (< 6 months of age) should be reserved for patients with persistent documented urine draining from the urachus or a documented abscess. Incidental (US) UR management remains a challenge and should be done with patient and family involvement to make the most informed decision. While surgical intervention has minimal risk and morbidity, it is performed unnecessarily in a large proportion of asymptomatic patients due to the unnecessary removal of non-epithelial containing urachal anomalies and the inability to predict which anomalies will undergo malignant transformation [1312].

3.19.1.9 Recommendation for management of urachal remnants

Recommendations	**Strength rating**
Urachal remnants (URs) with no epithelial tissue carry little risk of malignant transformation.	Strong
Asymptomatic and non-specific atretic urachal remnants can safely be managed non-operatively.	Strong
Urachal remnants incidentally identified during diagnostic imaging for non-specific symptoms should also be observed non-operatively since they tend to resolve spontaneously.	Strong

A small UR, especially at birth, may be viewed as physiological.	Strong
Urachal remnants in patients younger than 6 months are likely to resolve with non-operative management.	Strong
Follow-up: is necessary only when symptomatic for 6 to 12 months.	Strong
Surgical excision of URs solely as a preventive measure against later malignancy appears to have minimal support in the literature.	Strong
Only symptomatic URs should be safely removed by open or laparoscopic approach.	Strong
A voiding cystourethogram is only recommended when presenting with febrile UTIs.	Strong

*3.19.2 **Papillary tumours of the bladder in children and adolescents (Papillary urothelial neoplasm of low malignant potential or transitional cell carcinoma)***

3.19.2.1 Incidence

Papillary tumours of the bladder in children and adolescents are extremely rare and are different from papillary tumours in adults. A “grape-like” papillary tumour in young children will be more likely a rhabdomyosarcoma of the bladder, which are not the focus of this guideline. A papillary tumour in older children or adolescents will be more likely be a papillary urothelial neoplasm of low malignant potential (PUNLMP) [1313]. Children with risk factors, such as previous bladder surgery and immunosuppressive medication can also develop a nephrogenic adenoma of the bladder, also presenting as a papillary tumour of the bladder.

3.19.2.2 Differences and similarities of papillary tumours of the bladder in children and adults

Gender

The overall the risk of a papillary tumour in the bladder in paediatric and young adult patients is approximately double in males compared to females [1314].

3.19.2.3 Risk factors

The majority of these patients have no identifiable risk factors.

3.19.2.4 Presentation

The most common symptom at presentation is haematuria; other less common symptoms include abdominal pain, storage LUTS including frequency, dysuria and at times obstructive symptoms [1314].

3.19.2.5 Investigations and treatment

Ultrasound of the genitourinary tract is the first investigation of choice. It is an excellent screening tool and can often accurately diagnose the nature and location of lesion. In children and adolescents, a bladder US of the full bladder is more sensitive compared with adults due to reduced abdominal fat and thinner muscle layer [1315]. In the event of a need to differentiate the renal or bladder origin of the haematuria, a red blood cell morphology will reveal isomorphic blood cells, differentiating a bladder origin. Urine cytology can be performed, however it has very limited value likely due to the low-grade nature of these tumours in children. Cystoscopy should be reserved if a bladder tumour is suspected on imaging for simultaneous diagnosis and treatment, transurethral resection of the tumour. In children, cystoscopy requires general anaesthesia [1316].

3.19.2.6 Histology

All the lesions in the children and adolescent age-group are identified as papillary and over 85% are solitary [1315]. Papillary bladder tumours in patients younger than twenty years of age have low-grade non-invasive disease (WHO classification) [1317]. These findings let pathologists conclude that in children and adolescents, a papillary bladder tumour can be classified as Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP). PUNLMP has minimal or no cytological atypia and it differs from low grade transitional cell carcinoma (TCC) which has cytologic atypia, hyperchromatic nuclei and scattered mitosis [1318].

3.19.2.7 Additional treatment

Mitomycin C and Bacillus Calmette-Guérin have both been used in children but there is no evidence of their efficacy due to the rarity of TCC, and especially of high grade TCC [1314]. Hence, as per current evidence, there is no place for instillations in children.

3.19.2.8 Prognosis, recurrence and surveillance

The prognosis of papillary tumours of the bladder in children is overall good. The recurrence rate in children and adolescents varies from 8 to 15% [1313-1315]. Mean time to recurrence can vary from 11 to 29 months depending on the study, with recurrences occurring up to 90 months from diagnosis; though 64% occur in the first year [1314]. In certain cases, recurrences can be fairly aggressive [1315].

Strategies are based on the guidelines and protocols of papillary tumours of the bladder in adults. It is advised to follow-up children and adolescents with a history of a PUNLMP initially with a short interval of three to six months in the first year, and thereafter at least yearly with urinanalysis for haematuria and an US of the full bladder. In the event of sudden gross haematuria, the evaluation must be performed immediately. If the tumour was completely resected at primary surgery, standard follow-up cystoscopy is not necessary and may be reserved for children or adolescents with a high recurrence risk or suspected recurrence on bladder US [1315]. The exact duration of follow-up is unknown but this Panel recommends follow-up for at least five years.

Inflammatory myofibroblastic tumours of the bladder (IMTB) are rare with nearly 200 cases reported in the literature [1319, 1320]. Around 25% occur in children with a median age at diagnosis of 7.5 years and a median tumour size of 5.5 cm. Boys and girls are equally affected [1321]. Usually these tumours are benign, with only very few reported malignant cases [1322]. Treatment is mostly surgical with transurethral resection, but local resection, or partial cystectomy maybe needed in selected cases [1321, 1323]. Additionally, a conservative approach is reported [1324]. Histological examination is required to exclude other malignant tumours such as a rhabdomyosarcoma. In children, no recurrence has been reported so far. However due to the malignant potential and few recurrences in adults, follow-up the same as for papillary bladder tumours is recommended.

Eosinophilic cystitis

Though well described in adults, this inflammatory condition is rare in the paediatric population with less than 100 cases reported in the literature to date [1325]. Its etiology remains unknown, but is thought to be incited by IgE mediated attraction of eosinophils to bladder wall followed by mast cell degranulation. It has been linked to medications, specifically antibiotics such as penicillin, chemotherapeutic agents e.g. cyclophosphamide and mitomycin, and chronic bladder catheterisation [1326, 1327]. In children, as opposed to adults, males are more frequently afflicted with seven years being the mean age of presentation, however the condition can be seen throughout childhood even in LUTS [1325, 1328].

Irritative bladder symptoms such as dysuria, frequency, urgency and incontinence are the most frequent and can mimic UTI [1329]. Other symptoms include haematuria, suprapubic tenderness and systemic symptoms. Obstructive manifestations due to mass formation in the bladder wall can result in ureteral obstruction leading to hydro-ureteronephrosis, suprapubic mass in infants in addition to voiding dysfunction [1325, 1328, 1330].

Although associated with allergy only about a third of reported cases had a history of other allergic conditions whereas half had significant eosinophilia or eosinophiluria. Diagnosis is often delayed as symptoms of eosinophilic cystitis (EC) mimic other more common conditions such as UTI and LUTS and most patients will ultimately have undergone imaging studies such as ultrasound, VCUG, CT and MRI, which although not specially diagnostic for the condition, may show bladder wall thickening or even mass formation, with rhabdomyosarcoma constituting an important differential diagnosis. A high index of suspicion for the diagnosis should therefore be maintained when dealing with protracted urinary symptoms not responsive to conventional intervention. Definitive diagnosis can only be attained on tissue biopsy obtained by cystoscopy. Histologically, eosinophilic infiltration of lamina propria and muscularis are seen in acute phases with > 25 eosinophils per high power field considered to be significant [1325, 1328, 1330]. Management is not standardised; removal of any possible allergens is the obvious first step and there are reports of self-limiting course of the disease. However, empirical treatment with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A have been utilised and lead to resolution of symptoms in most cases. Partial cystectomy has been performed in circumscribed lesions that do not disappear spontaneously. No standard follow-up recommendations exist however surveillance is justified as recurrence has been reported in about a third of patients [1325, 1328].

Nephrogenic adenoma

Nephrogenic adenomas (NA) in children are rare benign lesions that usually occur in the setting of previous surgery or chronic irritation of urinary tract [1331]. These benign proliferative lesions are most commonly found in the bladder. There is a significant predominance of girls compared to boys (5:1). The exact pathogenesis is unknown. It is proposed to be a metaplastic process of native urothelium in response to chronic injury. Recent evidence suggest that they can be derived from renal tubular cells that shed, migrate, reimplant and proliferate within urothelial mucosa [1332]. Though they are known to occur concurrently with bladder cancer, there are no *de novo* cases of bladder cancer diagnosed after nephrogenic adenoma. Previous history of bladder surgery such as bladder augmentation or presence of chronic inflammation or irritation is important [1333]. Lesions tend to develop at sites prone to chronic catheterisation injury. Other risk factors include trauma, immunosuppression and radiation. They present with haematuria and storage LUTS with a papillary/ polypoid mass on cystoscopy. The recurrence rate is as high as 80% over 4 years [1331]. The final diagnosis

is established by cystoscopy and histopathological review of biopsy specimen. Treatment is excision either by transurethral resection which often requires reresections, partial cystectomy or open excision. Again no standard follow-up recommendations exist however regular follow-up with cystoscopy has been advocated especially for patients with augmented bladders as recurrence seem particularly high in this subgroup [1333].

3.19.2.9 Summary of evidence and recommendations for papillary tumours of the bladder in children

Summary of evidence	**LE**
Majority of paediatric patients have no identifiable risk factors for bladder tumours.	3
There is no evidence on intravesical therapy for bladder tumours in children and adolescents.	4
Prognosis of papillary tumours of the bladder in children is good overall.	3
Inflammatory myofibroblastic bladder tumours are usually benign.	3
Paediatric EC cases are in a third of cases associated with a history of allergic conditions and in 50% with significant eosinophilia or eosinophiluria.	4
Paediatric EC patients usually present with irritative and or obstructive urinary symptoms which can mimic UTI or LUTS thereby leading to delayed diagnosis.	4
In paediatric EC definitive diagnosis can only be attained on tissue biopsy obtained by cystoscopy.	4
In EC treatment with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A have been utilised and lead to resolution of symptoms in most cases.	4
No standard follow-up recommendations exist however surveillance is justified as recurrence has been reported in about a third of patients.	4
NA in children are rare benign lesions that usually occur in the setting of previous surgery or chronic irritation of urinary tract and mainly occurring in the bladder.	4
NA usually presents with haematuria and or storage LUTS and with a papillary/polypoid mass on seen on cystoscopy.	4
NA diagnosis is established by cystoscopy and histopathological review of biopsy specimen.	4
NA treatment is excision either by transurethral resection which often requires reresections, partial cystectomy or open excision.	4
NA recurrence rate is high thereby justifying regular follow-up.	4

Recommendations	**LE**	**Strength rating**
Ultrasound is the first investigation of choice for the diagnosis of paediatric bladder tumours.	3	Strong
Cystoscopy should be reserved if a bladder tumour is suspected on imaging for diagnosis and treatment.	3	Strong
After histological confirmation, inflammatory myofibroblastic bladder tumours should be resected locally.	4	Weak
Follow-up should be every 3-6 months in the first year, and thereafter at least annually with urinanalysis and an ultrasound for at least 5 years.	4	Weak
Have a high index of suspicion of eosinophilic cystitis (EC) in protracted urinary tract symptoms unresponsive to regular treatment.	4	Strong
Remove any possible allergens as the obvious first step in managing EC.	4	Strong
Eosinophilic cystitis can be managed medically with corticosteroids, antibiotics, anticholinergics, and antihistamines, in addition to cyclosporine A.	4	Weak
Manage nephrogenic adenoma (NA) by resection either transuretherally or by open excision.	4	Strong
Regular endoscopic follow-up especially for augmented patients with NA is justified.	4	Weak

*3.19.3 **Penile rare conditions***

Paediatric lesions of the penis are uncommon but an important part of the paediatric urological practice. The most common of these lesions are cystic penile lesions followed by vascular malformations and neurogenic lesions [1334]. Soft tissue tumours of the male external genitalia are uncommon, but have been described in the paediatric age group and can be malignant [1335].

3.19.3.1 Cystic lesions

- **Epidermal inclusion cysts** are the most common genital cystic lesion and can occur anywhere on the body in both men and women; in the penis it occurs most commonly over the penile shaft varying from 0.1 to 1 cm in diameter. Their epithelium is lined and filled with keratin. It is a painless swelling and can

present in the age group with a history of circumcision. Treatment by total surgical excision is mainly indicated for cosmetic or symptomatic (e.g. infection) reasons and should be performed without rupturing the cyst to avoid recurrence [1336].

- **Mucoid cyst of the penis** is synonymous with parameatal cyst or genitoperineal cyst of median raphe; they are midline developmental cysts arising from ectopic urethral mucosa filled with mucoid material. They present since birth but are usually detected during adolescence or later. They are usually asymptomatic developing over penile ventral surface around glans and require surgical removal for either cosmetic, functional or symptomatic reasons [1337].

- **Median raphe cysts** arise from incomplete closure of genital fold during embryogenesis; they are commonly diagnosed in the first decade of life but can present later as they tend to be asymptomatic [1338]. They are either unilocular or multilocular fluid containing cysts, with a mean size of 0.8 cm but cysts larger than 2 cm have also been reported [1339]. Cysts are centred in dermis, with no connection to urethra or epidermis. Histopathologically, there are 4 types: urethral (urothelium-like epithelium, account for 55% cases), epidermoid, glandular and mixed. They can be treated conservatively and can resolve spontaneously or persist. Cyst aspiration is associated with high risk of recurrence and surgical excision is the treatment of choice. Though most penile cysts are asymptomatic, they may get infected resulting in pain and tenderness. They can also present with ulceration, rupture and urinary obstruction if they are close to the urethral meatus. This along with cosmetic issues means that most caregivers and patients opt for surgical excision.

- **Smegmal cysts or smegmal pearls** can be a differential for the cysts above; they are a benign collection of smegma in the sub-preputial space in uncircumcised boys with anticipated spontaneous resolution [1340].

- **Dermoid cyst** are congenital, asymptomatic, firm, solitary, subcutaneous cystic lesions occurring commonly in the region of the corona involving the foreskin. Histopathologically they contain sweat and sebaceous glands with elements of hair and squamous epithelium. Pilosebaceous cysts have been described on the glans; they are benign and usually diagnosed after excision.

3.19.3.2 Vascular malformations

A broad classification of penile vascular lesions into haemangiomas and vascular malformations was proposed by Ramos in 1999 [1341]. **Haemangiomas** develop rapidly at birth and involute slowly; they also include **pyogenic granulomas** which are benign outgrowths of cutaneous capillary vessels formed usually from chronic irritation [1334]. The growth cycle of infantile haemangiomas is divided into early and late proliferative stages, followed by a slow involution phase, completing growth by nine months of age [1342]. Propranolol is currently first line treatment for infantile haemangiomas, the exact mechanism of action is unknown but can include inhibition of angiogenesis, vasoconstriction among others. The dose is in the range of 1.5-2.5 mg/kg, which needs to be continued for 12 to 18 months and then tapered through active or passive weaning to reduce risk of rebound growth [1342]. Other factors leading to rebound growth after propranolol treatment include deep haemangiomas, which occur in about 38% patients despite propranolol therapy, requiring local therapy such as topical timolol, pulsed dye laser or intralesional steroids. After twelve months, the median improvement with treatment is reported as 81% (range 70-90%) based on VAS scores of serial patient photographs.

Vascular malformations are congenital lesions of capillary, lymphatic and venous (or slow-flow) or arterial/arteriovenous (fast-flow) origin that enlarge slowly as the patient grows. These include **glomus tumours**, which are primarily congenital arteriovenous shunts that develop from thermo-regulatory glomus bodies (fastflow vascular malformations). Glomus tumours of the penis can arise on the glans penis, corpora of the penis and as periurethral masses, sometimes accompanied by glomus tumours of fingers and feet [1343]. These are usually asymptomatic at presentation or may have symptoms such as priapism, palpitation and perineal pain. Glomus tumours are benign despite exhibiting high grade nuclear polymorphism. Vascular malformations are usually benign and treated either with laser, sclerotherapy or surgical excision. However, glomus tumours specifically need surgical treatment and follow-up due to the risk of recurrence from incomplete excision [1344].

3.19.3.3 Neurogenic lesions

Penile neurofibroma is an extremely rare lesion arising from perineural and Schwann cells, and occurs usually with evidence of systemic neurofibromatosis or von Recklinghausen syndrome [1345]. They are treated successfully with complete excision [1334]. Rare cases of **malignant schwanomas** on the penis presumably secondary to malignant transformation of benign neurofibromas have been reported in boys with a strong family history of neurofibromatosis. This type of malignant degeneration of neurofibromatosis occurs in

reportedly 5-16% children [1345]. Hence, these patients require long-term follow-up due to risk of recurrence, new tumour formation and malignant transformation.

3.19.3.4 Soft tissue tumours of penis

Mesenchymal tumours are rare in the external genitalia and they require excision in order to differentiate between benign and malignant neoplasms. Histopathological characterisation is essential to ensure malignant tumours receive radical treatment with adjuvant therapy or close follow-up [1335].

Presentation is usually of a painless penile mass, that is non-tender and rubbery on examination. Ultrasound maybe useful in characterising the lesion but is not diagnostic; it can exclude urethral invasion if it is close to urethra [1335]. Once an excision biopsy is performed, if aggressive malignant components are found, a further wider resection may be needed.

Fibrosarcoma is a rare non-rhabdomyosarcoma soft tissue tumour that arises from fibrous tissue. The infantile form of **fibrosarcoma** is rare and those occurring on the penis are even rarer in the paediatric age-group. Surgical intervention has a favourable prognosis in the paediatric age group with long-term survival of 90% in sporadic cases [1346]. Myofibroma is a benign congenital lesion that occurs either as a solitary lesion or as a part of myofibromatosis with multiple soft tissue tumours. Excision is necessary for histological diagnosis [1335].

Primary penile **teratomas** are extremely rare subtype of congenital germ cell tumours, and they tend to be asymptomatic and are subdermal on US with no blood flow on Doppler [1347]. They need aggressive treatment with surgical resection due to their unpredictable behavior and unresponsiveness to chemotherapy. Mature teratomas are benign but immature teratoma or even mixed teratomas with immature components can turn malignant and have the potential to metastasise and recur.

3.19.3.5 Penile Lymphedema

Lymphedema in adults is usually secondary to malignancy or infectious disease affecting lymphatic drainage. In the paediatric age group, however, lymphedema is usually primary and generally very rare, affecting 1.2 per 100.000 persons under the age of 20 years [1348]. Of these, only a very small fraction relates to the genital region. Regardless of underlying aetiology, inefficient lymphatic drainage leads to accumulation of subcutaneous lymph which causes tissue swelling and inflammation. This in turn stimulates adipose deposition and fibrosis further exacerbating enlargement. With time the edematous tissue becomes vulnerable to infection, chronic cutaneous changes and disfigurement [1349]. Additionally, when occurring in the genital region urological complications may ensue; such as phimosis, haematuria, bleeding, bladder outlet obstruction, pain, dysuria, lymphorrhea and severe psychological distress due to resultant deformity [1350, 1351].

In the largest cohort of male genital oedema in the paediatric age group, 92% of cases were primary; of these only 25% had a discernable familial or syndromic association such as Noonan syndrome, lymphedemadistichiasis or Milroy disease [1350]. Secondary genital lymphedema in children has been reported after inguinal surgery, and non-caseating granulomatous lymphangitis as seen with metastatic Crohn's disease [1350-1352]. Average age of onset was reported to be 4.5 ± 6.3 years with 61% presenting in infancy, 13% in childhood and the remaining 26% in adolescence. Edema is usually penoscrotal in 72%, isolated scrotal in 24% and very rarely confined exclusively to the penis in 4%. Moreover, concomitant lower limb edema is the rule in two thirds of cases [1350].

There is no general consensus on diagnostic work-up of these patients. History and physical examination (including family history) is usually sufficient. However lymphoscintigraphy can be used as a confirmatory test, more so for limb than genital edema where results can be difficult to interpret [1350]. Ultrasonography is nonspecific, but has been advocated by some to exclude secondary lymphedema by examining the patency of iliac and caval vessels [1353]. Magnetic resonance imaging is useful to exclude other differential diagnoses such as other venous or lymphatic anomalies [1350].

Conservative treatment is the accepted first-line treatment. The mainstay is compression therapy to maintain and prevent further swelling. This can be achieved by compression stockings and undergarments. Additionally, close observation and protection of the skin to prevent excoriations and infection is essential [1350, 1353]. Compression therapy is however, less effective on genital oedema than it is on limb edema, especially in growing children. When conservative management fails, and especially in symptomatic cases, or in patients with functional impairment, surgical debulking may be necessary. This can either take the form of circumcision in cases where the foreskin is affected or excision of affected skin and subcutaneous tissues with restructuring and contouring for optimal cosmetic outcome. Complete skin excision and grafting may also be required

[1350-1353]. Surgical management can be challenging and needs to be restricted to patients with significant symptoms. Complications include recurrences, continuous lymphatic leakage, haematoma, infection and poor cosmetic outcome [1348, 1353, 1354].

Summary of evidence	LE
Cystic penile lesions are the commonest paediatric penile lesions followed by vascular malformations and neurogenic lesions.	3
Neurofibroma patients require long-term followup due to risk of recurrence, new tumour formation and malignant transformation.	3
Mesenchymal tumours are rare and require excision in order to differentiate between benign and malignant neoplasms.	3

Recommendations	LE	Strength rating
Treatment of penile cystic lesions is by total surgical excision, it is mainly indicated for cosmetic or symptomatic (e.g. infection) reasons.	4	Weak
Propranolol is currently first line treatment for infantile hemangiomas.	2b	Strong
Conservative management is the first-line treatment for penile lymphedema.	4	Strong
In symptomatic cases or in patients with functional impairment, surgical intervention may become necessary for penile lymphedema.	4	Weak

3.20 Paediatric urological trauma

Trauma is the leading cause of morbidity and mortality in children and is responsible for more childhood deaths than the total of all other causes [1355]. In about 3% of children seen at paediatric hospital trauma centres, there is significant involvement of the genitourinary tract [1356]. This is caused by either blunt injuries from falls, car accidents, sports injuries, physical assault, sexual abuse, or penetrating injuries, usually due to falls onto sharp objects or from gunshot or knife wounds.

*3.20.1 **Paediatric renal trauma***

3.20.1.1 Epidemiology, aetiology and pathophysiology

In blunt abdominal trauma, the kidney is the most commonly affected organ, accounting for about 10% of all blunt abdominal injuries [1355].

Children are more likely than adults to sustain renal injuries after blunt trauma because of their anatomy. Compared to an adult kidney, a child's kidney is larger in relation to the rest of the body and often retains foetal lobulations, so that blunt trauma is more likely to lead to a local parenchymal disruption. The paediatric kidney is also less well protected than the adult kidney. Children have less peri-renal fat, much weaker abdominal muscles, and a less ossified and therefore much more elastic and compressible thoracic cage [1357].

Blunt renal trauma is usually a result of sudden deceleration of the child's body, particularly due to sport accidents, falls, and contact with blunt objects. Deceleration or crush injuries result in contusion, laceration or avulsion of the less well-protected paediatric renal parenchyma.

3.20.1.2 Classification systems

Renal injuries are classified according to the kidney injury scale of the American Association for the Surgery of Trauma (Table 7) [1358].

Table 7: Renal injury classified according to the kidney injury scale of the American Association for the Surgery of Trauma [1358]

Grade	Type of injury	Description
I	Contusion	Non-visible or visible haematuria
	Haematoma	Normal urological studies
II	Haematoma	Non-expanding subcapsular haematoma
	Laceration	Laceration of the cortex of < 1.0 cm
III	Laceration	Laceration > 1.0 cm without rupture of collecting system
IV	Laceration	Through the cortex, medulla and collecting system
	Vascular	Vascular injury
V	Laceration	Completely shattered kidney
	Vascular	Avulsion of the renal hilum

3.20.1.3 Diagnostic evaluation

In a child who has sustained blunt abdominal trauma, renal involvement can often be predicted from the history, physical examination and laboratory evaluation. Renal involvement may be associated with abdominal or flank tenderness, lower rib fractures, fractures or vertebral pedicles, trunk contusions and abrasions, and haematuria.

3.20.1.3.1 Haematuria

Haematuria may be a reliable finding. In severe renal injuries, 65% suffer visible haematuria and 33% non-visible, while only 2% have no haematuria at all [1359].

The radiographic evaluation of children with suspected renal trauma remains controversial. Some centres rely on the presence of haematuria to diagnose renal trauma, with a threshold for renal involvement of 50 RBCs/HPF. Although this may be a reliable threshold for significant non-visible haematuria in trauma, there have been many reports of significant renal injuries that manifest with little or even no blood in the urine [1360]. It is therefore compulsory to consider all the clinical aspects involved, including the history, physical examination, consciousness of the child, overall clinical status and laboratory findings to decide on the diagnostic algorithm and whether or not a child needs further imaging studies.

3.20.1.3.2 Blood pressure

It is important to consider that children, unlike adults, are able to maintain their blood pressure, even in the presence of hypovolaemia, due to compliance of the vascular tree and mechanisms for cardiac compensation [1361]. As blood pressure is an unreliable predictor of renal involvement in children, some centres recommend imaging of the urinary tract in children with any degree of haematuria following significant abdominal trauma.

3.20.1.3.3 Choice of imaging method

Nowadays, CT is the best imaging method for renal involvement in children. Computed tomography scanning is the cornerstone of modern staging of blunt renal injuries especially when it comes to grading the severity of renal trauma.

Computed tomography scanning is quite rapid and usually performed with the injection of contrast media. To detect extravasation, a second series of images is necessary since the initial series usually finishes 60 seconds after injection of the contrast material and may therefore fail to detect urinary extravasation. In acute trauma, US may be used as a screening tool and for reliably following the course of renal injury. However, US is of limited value in the initial and acute evaluation of trauma. The standard intravenous pyelogram (IVP) is a good alternative imaging method if a CT scan is not available. It is superior to US but not as good as CT scanning for diagnostic purposes.

3.20.1.4 Disease management

The modern management of trauma is multidisciplinary, requiring paediatricians, emergency physicians, surgeons, urologists, and other specialties as required.

Non-surgical conservative management with bed rest, fluids and monitoring has become the standard approach for treating blunt renal trauma. Even in high-grade renal injuries, a conservative approach is effective and recommended for stable children. However, this approach requires close clinical observation, serial imaging, and frequent re-assessment of the patient's overall condition. Therefore, a good initial trauma CT with delayed images to check for urinary extravasation is recommended since this may prevent repeat ionising scans. In stable patients with grade 2 or higher lesions a close follow-up with US 48 to 72 hours after the initial scan is sufficient and should be considered before repeating a CT scan [1362]. A systematic review supports application of conservative management protocols also to high-grade blunt paediatric renal trauma. At this time, emergent operative intervention only for haemodynamic instability is recommended. Minimally invasive interventions including angio-embolisation, stenting, and percutaneous drainage should be used when indicated [1363]. Absolute indications for surgery include persistent bleeding into an expanding or unconfined haematoma. Relative indications for surgery are massive urinary extravasation and extensive non-viable renal tissue [1364]. A recently published meta-analysis concluded with the following recommendations: (1) In paediatric patients with blunt renal trauma of all grades, non-operative management vs. operative management in haemodynamically stable patients is strongly recommended. (2) In haemodynamically stable paediatric patients with high-grade (AAST grade III-V) renal injuries, angio-embolisation vs. surgical intervention for ongoing or delayed bleeding is strongly recommended; and, (3) In paediatric patients with renal trauma, routine blood pressure checks to diagnose hypertension is recommended in the long-term follow-up [1365]. However, long-term data on the risk of developing hypertension is lacking.

3.20.1.5 *Recommendations for the diagnosis and management of paediatric renal trauma*

Recommendations	Strength rating
Use imaging in all children who have sustained a blunt or penetrating trauma with any level of haematuria, especially when the history reveals a deceleration trauma, direct flank trauma or a fall from a height.	Strong
Use rapid spiral computed tomography with delayed images scanning for diagnostic and staging purposes.	Strong
Manage most injured kidneys conservatively.	Strong
Offer surgical intervention in case of haemodynamic instability and a Grade V renal injury.	Strong

3.20.2 ***Paediatric ureteral trauma***

Injuries to the ureter are rare. The ureter is well protected; the upper part is protected by its close approximation to the vertebral column and paraspinal muscles and the lower part by its route through the bony pelvis. In addition, the ureter is a small target, and both flexible and mobile. This also means that ureteral injuries are caused more often by penetrating trauma than blunt trauma [1366]. Since the ureter is the sole conduit for urinary transport between the kidney and the bladder, any ureteral injury can threaten the function of the ipsilateral kidney.

3.20.2.1 *Diagnostic evaluation*

Since there are no classical clinical symptoms suggestive of ureteral trauma, it is important to carry out a careful diagnostic work-up using different imaging modalities. Unfortunately, initial imaging studies, such as IVP and routine CT scans, are unreliable. A study of eleven disruptions of the ureteropelvic junction found that 72% had a normal or non-diagnostic IVP on initial studies [1366]. Diagnostic accuracy of CT scanning can be improved by performing a delayed CT scan up to ten minutes after injection of the contrast material [1367]. The most sensitive diagnostic test is a retrograde pyelogram.

Quite a few patients present several days after the injury, when the urinoma produces flank and abdominal pain, nausea and fever.

Due to symptoms being often vague, it is important to remain suspicious of a potential undiagnosed urinary injury following significant blunt abdominal trauma in a child.

3.20.2.2 *Management*

Immediate repair during abdominal exploration is rare. Minimally invasive procedures are the method of choice, especially since many ureteral injuries are diagnosed late after the traumatic event. Percutaneous or nephrostomy tube drainage of urinomas can be successful, as well as internal stenting of ureteral injuries [1368]. If endoscopic management is not possible, primary repair of partial lacerations should be followed by internal stenting. The management of complete lacerations, avulsions or crush injuries depends on the amount of ureter lost and its location. If there is an adequate healthy length of ureter, a primary ureteroureterostomy can be performed. If primary re-anastomosis is not achievable, distal ureteral injuries can be managed using a psoas bladder hitch, Boari flap or even nephropexy. Proximal injuries can be managed using transureteroureterostomy, auto-transplantation or ureteral replacement with bowel or appendix [1369].

3.20.2.3 *Recommendations for the diagnosis and management of paediatric ureteral trauma*

Recommendations	Strength rating
Diagnose suspected ureteral injuries by retrograde pyelogram.	Strong
Manage ureteral injuries endoscopically, using internal stenting or drainage of an urinoma, either percutaneously or via a nephrostomy tube.	Weak

3.20.3 ***Paediatric bladder injuries***

The paediatric bladder is less protected than the adult bladder, and is therefore more susceptible to injuries than the adult bladder, especially when it is full, due to:

- Its higher position in the abdomen and its exposure above the bony pelvis.
- The fact that the abdominal wall provides less muscular protection.
- The fact that there is less pelvic and abdominal fat surrounding the bladder to cushion it in trauma.

Blunt trauma is the most common cause of significant bladder injury. In adults, bladder injury is often associated with pelvic fractures. This is less common in children because the paediatric bladder sits above

the pelvic ring. In a large prospective study, only 57% of children with pelvic fractures also had a bladder injury compared to 89% of adults [1370].

3.20.3.1 Diagnostic evaluation

The characteristic signs of bladder injury are suprapubic pain and tenderness, an inability to urinate, and visible haematuria (95% of injuries). Patients with a pelvic fracture and visible haematuria present with a bladder rupture in up to 45% of cases [1371].

The diagnosis of bladder rupture can be difficult in some cases. The bladder should be imaged both when fully distended and after drainage using standard radiography or a CT scan. The best results can be achieved by retrograde filling of the bladder using a catheter. Despite advances in CT imaging, the bladder must still be filled to capacity to accurately diagnose a possible bladder injury [1372].

Blunt injuries to the bladder are categorised as:

- contusions with damage to the bladder mucosa or muscle, without loss of bladder wall continuity or extravasation;
- ruptures, which are either intraperitoneal or extraperitoneal.

Intraperitoneal bladder ruptures are more common in children because of the bladder's exposed position and the acute increase in pressure during trauma. These cause the bladder to burst at its weakest point, i.e. the dome. Extraperitoneal lesions occur in the lower half of the bladder and are almost always associated with pelvic fractures. A cystogram will show extravasation into the perivesical soft tissue in a typical flame pattern and the contrast material is confined to the pelvis.

3.20.3.2 Management

Contusions usually present with varying degrees of haematuria and are treated with catheter drainage alone.

3.20.3.2.1 Intraperitoneal injuries

The accepted management of intraperitoneal bladder ruptures is open surgical exploration and primary repair. Post-operative drainage with a suprapubic tube is mandatory. Recent data suggest that transurethral drainage may be as effective, with fewer complications, resulting in shorter periods of diversion [1373]. Usually, after about seven to ten days, a repeat cystogram is performed to ensure healing is taking place properly.

3.20.3.2.2 Extraperitoneal injuries

Non-operative management with catheter drainage for seven to ten days alone is the method of choice for extraperitoneal bladder rupture. However, if there are bone fragments within the bladder, these must be removed and the bladder must then be repaired and drained, according to the principles for treating intraperitoneal ruptures [1374].

3.20.3.3 Recommendations for the diagnosis and management of paediatric bladder injuries

Recommendations	Strength rating
Use retrograde cystography to diagnose suspected bladder injuries.	Strong
Ensure that the bladder has been filled to its full capacity and an additional film is taken after drainage.	Strong
Manage extra-peritoneal bladder ruptures conservatively with a transurethral catheter left in place for seven to ten days.	Strong
Do not delay treatment of intra-peritoneal bladder ruptures by surgical exploration and repair as well as post-operative drainage for seven to ten days.	Strong

3.20.4 ***Paediatric urethral injuries***

Except for the penile part of the urethra, the paediatric urethra is quite well protected. In addition, its shape and elasticity mean the urethra is seldom injured by trauma. However, a urethral injury should be suspected in any patient with a pelvic fracture or significant trauma to the perineum until confirmed otherwise by a diagnostic work-up.

3.20.4.1 Diagnostic evaluation

Patients with suspected urethral trauma and pelvic fractures usually present with a history of severe trauma, often involving other organ systems.

Signs of urethral injury are blood at the meatus, visible haematuria, and pain during voiding or an inability to void. There may also be perineal swelling and haematoma involving the scrotum. A rectal

examination to determine the position and fixation of the prostate is important in any male with a suspected urethral injury. The prostate, as well as the bladder, may be displaced up out of the pelvis, especially in membranous urethral trauma.

Radiographic evaluation of the urethra requires a retrograde urethrogram. It is important to expose the entire urethral length, including the bladder neck. If a catheter has already been placed by someone else and there is suspected urethral trauma, the catheter should be left in place and should not be removed. Instead, a small infant feeding tube can be placed into the distal urethra along the catheter to allow the injection of contrast material for a diagnostic scan [1375].

3.20.4.2 Disease management

Since many of these patients are unstable, the urologist's initial responsibility is to provide a method of draining and monitoring urine output.

A transurethral catheter should only be inserted if there is a history of voiding after the traumatic event, and if a rectal and pelvic examination, as described above, has not suggested a urethral rupture. If the catheter does not pass easily, an immediate retrograde urethrogram should be performed.

A suprapubic tube may be placed in the emergency department percutaneously, or even in the operating room, if the patient has to undergo immediate exploration because of other life-threatening injuries.

There are often no associated injuries with a bulbous urethral or straddle injury and management is therefore usually straightforward. In these cases, a transurethral catheter is the best option for preventing urethral bleeding and/or painful voiding [1376].

The initial management of posterior urethral injuries remains controversial, mainly regarding the long-term results with primary realignment compared to simple suprapubic drainage with later reconstruction.

The main goals in the surgical repair of posterior urethral injuries are:

- Providing a stricture-free urethra.
- Avoiding the complications of urinary incontinence and impotence.

Suprapubic drainage and late urethral reconstruction was first attempted because immediate surgical repair had a poor outcome, with significant bleeding and high rates of incontinence (21%) and impotence in up to 56% of cases [1377]. In adults, a study of the success rates of delayed repair reported re-structure rates of 11-30%, continence rates of 90-95% and impotence rates of 62-68% [1378]. However, in children, there is significantly less experience with delayed repair. The largest paediatric series of delayed repair in 68 boys reported a success rate of 90% [1379]. Another study reported strictures and impotence in 67% of boys, although all the boys were continent [1186]. A recently published follow-up study on 15 patients who underwent delayed urethroplasty for blunt urethral trauma during childhood reported high long-term success rates with a low rate of long-term urinary and sexual dysfunction in adulthood [1380].

An alternative to providing initial suprapubic drainage and delayed repair is primary realignment of the urethra via a catheter. The catheter is usually put in place during open cystostomy by passing it from either the bladder neck or meatus and through the injured segment. In a series of fourteen children undergoing this procedure, this resulted in a stricture rate of 29% and incontinence in 7% of patients [1381].

3.20.4.3 Recommendations for the diagnosis and management of paediatric trauma

Recommendations	Strength rating
Assess the urethra by retrograde urethrogram in case of suspected urethral trauma.	Strong
Perform a rectal examination to determine the position of the prostate.	Strong
Manage bulbous urethral injuries conservatively with a transurethral catheter.	Strong
Manage posterior urethral disruption by either: • primary reconstruction; • primary drainage with a suprapubic catheter alone and delayed repair; • primary re-alignment with a transurethral catheter.	Weak

3.21 Peri-operative fluid management

*3.21.1 **Epidemiology, aetiology and pathophysiology***

Children have a different total body fluid distribution, renal physiology and electrolyte requirements, as well as weaker cardiovascular compensation mechanisms, compared to adults [1382]. During development, children have a high metabolic rate and lower fat and nutrient stores which means they are more susceptible to metabolic disturbances caused by surgical stress [1383]. The metabolic response to anaesthesia and surgery in infants and children is related to the severity of the operation [1384].

*3.21.2 **Disease management***

3.21.2.1 Pre-operative fasting

Pre-operative fasting has been advocated for elective surgery to avoid the complications associated with pulmonary aspiration during induction of anaesthesia. New regimens include a 30-60 minute limitation for clear liquids [1385, 1386] without increased risk of pulmonary aspiration [1387]. Several studies have shown that fasting times in clinical practice often exceed the guidelines with average fasting times of 6-10 hours [1386-1388]. Compared to adults, children have a higher metabolic rate and low glycogen stores and impaired gluconeogenesis, which makes hypoglycaemia an important issue to consider, especially in children < 36 months old [1386]. Therefore, it is important to prevent too long fasting times. Clear-liquid carbohydrate drinks have been proposed to reduce these fasting times [1389].

Table 8 provides the current six, four and one hour guidelines for pre-operative fasting for elective surgery [1386, 1388].

Table 8: Pre-operative fasting times for elective surgery

Ingested material	Minimum fasting period (hours)
Clear liquids	1
Breast milk	4
Light meal	6

3.21.2.2 Maintenance therapy and intra-operative fluid therapy

Generally, the anaesthetist is responsible for intra-operative management and the surgeon is responsible for post-operative instructions. The goal of intra-operative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid; this maintains adequate intravascular volume, cardiac output and oxygen delivery to tissues at a time when normal physiological functions have been altered by surgical stress and anaesthetic agents.

In recent years new strategies for maintenance and replacement fluid management have been developed and this has changed intra-operative fluid management significantly. The main goal of intra-operative fluid management is to maintain a normal extracellular fluid volume (EFV). During the intra-operative period fluid deficits may be induced by blood loss or pre-operative fasting. These fluid deficits can be replaced by balanced isotonic electrolyte solutions to restore a normal EFV. It is recommended that maintenance intravenuous (IV) fluids should consist of balanced isotonic solutions with appropriate potassium chloride and dextrose in order to decrease the risk of hyponatraemia development [1390]. No increased risk for hypernatraemia, fluid overload with aedema and hypertension, and hyperchloremic acidosis was found, which was always feared for isotonic solutions [1390].

When children are clinically unstable due to third-space losses, these losses should be replaced with crystalloids (normal saline or Ringer's lactate). Third-space losses may vary from 1 mL/kg/h for a minor surgical procedure to 15-20 mL/kg/h for major abdominal procedures, or even up to 50 mL/kg/h for surgery of necrotising enterocolitis in premature infants. When this fluid management is insufficient replacement management with colloids (albumin, gelatine and hydroxyethyl starch [HES]) should be adopted, using a restrictive approach [1391].

Clinical guidelines have been proposed by Sümpelmann *et al*. [1391] regarding intra-operative fluid management (Table 9).

Table 9: Intra-operative fluid management

	Solution for infusion	Initial/repeated dose
Background infusion	Balanced isotonic solution + 1-2% glucose	10 mL/kg/h
Fluid therapy	Balanced isotonic solution	X 10-20 mL/kg
Volume therapy	Albumin, Gelatine, hydroxyethyl starch	X 5-10 mL/kg
Transfusion	Red blood cells, fresh frozen plasma, platelets	X 10 mL/kg

3.21.2.3 Post-operative feeding and fluid management

It is not obligatory to check serum chemistry after uncomplicated surgery in children with normal pre-operative renal and hepatic function. However, if oral intake has been postponed for > 24 hours (e.g. as in intestinal surgery), there is an increased risk of electrolyte abnormalities, requiring further assessment and subsequent

management, particularly with potassium. Post-operative findings, such as decreased bowel movements and ileus, may be signs of hypokalaemia.

Children who undergo interventions to relieve any kind of obstructive diseases deserve particular attention, especially due to the risk of polyuria as a result of post-obstructive diuresis [1392]. In children who develop polyuria, it is important to monitor fluid intake and urine output, as well as renal function and serum electrolytes. If necessary, clinicians should not hesitate in consulting with a paediatric nephrologist.

In children who have undergone non-abdominal surgery, studies have suggested that gastric motility returns to normal one hour after emergence from anaesthesia [1393]. Early post-operative intake of fluid in children who have undergone minor or non-abdominal urological surgery is associated with reduced post-operative vomiting and lower opioid use [1394] and is therefore encouraged.

In abdominal surgery the enhanced recovery after surgery (ERAS) protocol has been implemented in the paediatric population following its success in adults [1389, 1395]. The ERAS protocol is a multimodal approach to prevent the post-operative effects of the surgical stress response. This protocol includes pre- and intraoperative element such as minimal pre-operative fasting and careful intra-operative fluid management, and also focuses on post-operative care. The post-operative ERAS protocol suggests starting clear fluid intake on the evening of surgery and a normal diet the day after surgery and thereby early discontinuation of IV fluids. Further focus is on early mobilisation, preventing epidurals and omitting or early removal of external tubes [1389, 1395].

The implementation of an ERAS protocol has resulted in shorter length of hospital stays, faster bowel recovery and opioid-free post-operative need [1389, 1395, 1396]. When implementing ERAS in children with neurological abnormalities special attention should be given to bowel management with pre-operative treatment of constipation and early post-operative continuation of routine bowel management.

3.21.3 Summary of evidence and recommendations for the management of peri-operative fluid management

Summary of evidence	LE
Children are not simply smaller physiological versions of adults. They have their own unique metabolic features, which must be considered during surgery.	2
During the intra-operative period balanced isotonic electrolyte solutions can be used to maintain a normal extracellular fluid volume.	1
Following abdominal surgery ERAS protocols can be used to reduce recovery times and complications.	1

Recommendations	Strength rating
Ensure shorter pre-operative fasting periods for elective surgeries (up to one hour for clear liquids).	Strong
Use enhanced recovery after surgery protocols for abdominal surgery in children with normal bowel movement.	Strong
Use isotonic solutions in hospitalised children because they are at high risk of developing hyponatraemia.	Strong
Assess the baseline and daily levels of serum electrolytes, glucose, urea and/or creatinine in every child who receives intravenous fluids, especially in intestinal surgery (e.g. ileal augmentation), regardless of the type of solution chosen since there is an increased risk of electrolyte abnormalities in children undergoing such surgery.	Strong
Start early oral fluid intake in all patients scheduled for minor surgical procedures.	Strong

3.22 Post-operative pain management: general information

3.22.1 Epidemiology, aetiology and pathophysiology

The provision of adequate pain control requires proper pain evaluation, accurate choice of drug and route of administration, and consideration of age, physical condition and type of surgery and anaesthesia [1397].

Traditional medical beliefs that neonates are incapable of experiencing pain have now been abandoned following recent and better understanding of how the pain system matures in humans, better pain assessment methods and a knowledge of the clinical consequences of pain in neonates [1398, 1399]. Many studies have indicated that deficient or insufficient analgesia may be the cause of future behavioural and somatic sequelae [1400, 1401]. Our current understanding of pain management in children depends fully on the belief that all children, irrespective of age, require adequate pain treatment.

*3.22.2 **Diagnostic evaluation***

Assessment of pain is the first step in pain management. Several pain assessment tools have been validated according to the child's age, cultural background, mental status, communication skills and physiological reactions [1402]. Depending on the child's age, the 0-10 Numeric Rating Scale, Faces Revised Pain Scale or Colour Analog Scale, for example, can be used [1403]. One of the most important topics in paediatric pain management is informing and involving the child and caregivers during this process. Patient-family-controlled-analgesia is the preferred pain management in the hospital and at home if provided with the correct information [1403, 1404].

*3.22.3 **Disease management***

3.22.3.1 Drugs and route of administration

Pre-emptive analgesia is an important concept that aims to induce the suppression of pain before neural hypersensitisation occurs [1405]. Regional anaesthesia are given intra-operatively which can include a regional nerve block, caudal blocks or local wound infiltration and has proven to reduce the need for post-operative analgesia [1406]. The WHO's 'pain ladder' is a useful tool for the pain management strategy [1407]. A three level strategy seems practical for clinical use. Post-operative management should be based on sufficient intraoperative pre-emptive analgesia with regional or caudal blockade followed by balanced analgesia. Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are the drugs of choice at the first level. As they become insufficient to prevent pain, weak and strong opioids are added to oral drugs to achieve balanced analgesia. Every institute must build their own strategy for post-operative analgesia. A proposed strategy for postoperative analgesia may be as follows:

1. Intra-operative regional or caudal block.
2. Paracetamol + NSAID.
3. Paracetamol + NSAID + weak opioid (e.g. tramadol or codeine).
4. Paracetamol + NSAID + strong opioid (e.g. morphine, fentanyl, oxycodone or pethidine).

The use of opioids in children has long held a standard role in the post-operative management of pain. Increased recognition of the adverse effects of opioids and prolonged opioid dependency demand a balanced intra-operative administration of opioids [1403, 1408]. Intra-operative adequate dosage of paracetamol and NSAIDs results in a decrease in opioid requirement in children [1409, 1410]. Furthermore, opioid awareness among physicians could reduce opioid use. When prescribing lower opioid dosage, this did not increase pain scores in urological outpatient surgeries [1411]. Caution is necessary to take account of renal function when using NSAIDs. Paediatric dependent dosages for most common used pain medication can be found in this publication [1412].

3.22.3.2 Circumcision

Circumcision requires anaesthesia and proper pain management [1413]. Potential analgesic interventions during circumcision include the use of a dorsal penile nerve block (DPNB) or ring block, topical anaesthetics (e.g. lidocaine-prilocaine cream, or 4% liposomal lidocaine cream), and sucrose preferably in combination [1406, 1412]. Caudal blockade methods have similar efficacy compared to DPNB. However, caregivers should be informed about the more frequent incidence of post-operative motor weakness and micturition problems [1414]. Ultrasound guidance can be used [1412].

3.22.3.2.1 Penile, inguinal and scrotal surgery

Caudal blocks and peripheral nerve blocks (DPNB and pudendal) are commonly used methods for analgesia following surgery for hypospadias. Several agents with different doses, concentrations and administration techniques have been used and shown to be adequate. Overall post-operative pain scores were lower with pudendal nerve blocks. No increase in post-operative complications was seen with these types of blocks [1406, 1415, 1416]. Severe bladder spasms caused by the presence of the bladder catheter may sometimes cause more problems than pain and is managed with antimuscarinic medications. For inguinoscrotal surgery, various regional anaesthesia methods have been investigated, such as transversus abdominis plane block, ilioinguinal/iliohypogastric nerve blocks and caudal blocks. All have been shown to have adequate postoperative analgesic properties. Additional local anaesthetics such as clonidine or dexmedetomidine may improve results [1406].

3.22.3.3 Bladder and kidney surgery

Continuous local infusion reduces the need for post-operative opioids [1417-1419], as well as systemic (intravenous) application of analgesics [1420], has been shown to be effective. Ketorolac is an effective agent that is underused. It decreases the frequency and severity of bladder spasms and the length of post-operative hospital stay and costs [1421, 1422]. Open kidney surgery is particularly painful because all three muscle layers

are cut during conventional loin incision. A dorsal lumbotomy incision may be a good alternative because of the shorter post-operative hospital stay and earlier return to oral intake and unrestricted daily activity [1423]. Caudal and paravertebral blocks continuous epidural analgesia, as well as rectus sheath and transversus abdominis plane blocks have decreased post-operative morphine requirement after abdominal and renal surgery [1424-1426]. For laparoscopic approaches, intra-peritoneal spraying of local anaesthetic before incision of the perirenal fascia may be beneficial [1427].

*3.22.4 **Summary of evidence and recommendations for the management of post-operative pain***

Summary of evidence	LE
Adequate paracetamol and NSAIDs use reduces opioid need post-operatively.	1
Pain may cause behavioural and somatic sequelae.	3
Every institute must develop their own well-structured strategy for post-operative analgesia.	4

Recommendations	Strength rating
Prevent/treat pain in children of all ages.	Strong
Evaluate pain using age-compatible assessment tools.	Strong
Inform patients and caregivers accurately.	Strong
Use pre-emptive and balanced analgesia in order to decrease the side effects of opioids.	Strong

3.23 Basic principles of laparoscopic surgery in children

*3.23.1 **Epidemiology, aetiology and pathophysiology***

The use of laparoscopy and robot-assisted laparoscopic surgery is rapidly increasing and has gained widespread acceptance for many urological surgeries in children. Diagnostic laparoscopy for undescended testis, nephrectomy, heminephrectomy, varicocelectomy, pyeloplasty and ureteral reimplantation are some of the indications which are commonly being performed. This expanding scope related to technological advancements allows surgeons to perform more complex procedures in a minimally invasive fashion even in infants and younger children. Generally, well established benefits of minimally invasive surgery are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery [861]. Additional advantages of robotic surgery over conventional laparoscopy include ergonomics, 3D vision, better manoeuvrability, decreased tremor and easy learning curve. Limitations to be considered are increased operative time, smaller working space at young age, cost and experience of the surgeon and anaesthesiologist. While the success and complication rates are comparable for nephrectomy and pyeloplasty (see chapter 3.13.3.2) advantages of laparoscopy and robotic surgery for ureteral reimplantation have not been proven and this can only be recommended for experienced centres (see chapter 3.14.3.2.3).

As worldwide experience increases, there is an accumulating awareness about the physiological consequences related to intra- and retroperitoneal carbon dioxide (CO_2) insufflation in children. In contrast to traditional open surgery pneumoperitoneum may have physiological responses which require close monitoring during surgery and should be taken seriously.

*3.23.2 **Technical considerations and physiological consequences***

3.23.2.1 Pre-operative evaluation

Laparoscopy in children requires specific anaesthetic precautions. Physiological effects of CO_2 pneumoperitoneum, positioning of the patient and in potentially increased operative time need to be considered by the anaesthesiology team. Therefore, a detailed medical examination and risk assessment is mandatory pre-operatively. Especially cardiac and pulmonary system should be assessed since increased intra-abdominal pressure may lead to decreased ventricular preload [1428].

3.23.2.2 Abdominal insufflation

Abdominal insufflation is the main principle of laparoscopic surgery to create working space for the surgeon. Carbon dioxide is the most commonly used insufflant in laparoscopic centres throughout the world. Other alternatives reported are nitrous oxide, helium, argon and air. However, CO_2 is considered to be the best available gas as it is colourless, cheap, has high solubility in the vascular system [1429] and is excreted by the pulmonary system making it the safest option. Smaller children and infants absorb more CO_2 than older children [1430], suggesting the need for more attention both during and early after laparoscopic surgery for these children.

Most complications of laparoscopy are attributable to gaining access to the abdominal cavity. One study reporting complications of > 5,400 paediatric laparoscopic surgeries showed that there was an overall complication rate of 5.3% of which 4.2% were related to problematic insufflation (subcutaneous emphysema, gas embolism, injury to the organs and vascular structures, mis-insufflation etc.) [1431]. There are two main and well-established techniques for initial access to the abdomen or retroperitoneum: open technique (Hasson) and Veress needle. Studies comparing these two different access techniques in paediatric laparoscopic urological procedures showed similar complication rates [1432]. The vast majority of the complications were minor and related to lack of surgical experience. Particularly in infants and smaller children, the open access technique is recommended by the Panel to reduce the chance of complications.

Elasticity of the abdominal wall is age-related and is higher in infants and small children compared to older children [1433].

Pneumoperitoneal pressure (PnP in mmHg) is one of the critical points that needs to be carefully considered by laparoscopic surgeons. A recent RCT compared two different pneumoperitoneal pressure groups (6-8 mmHg vs. 9-10 mmHg) in infants less than 10 kg [1434]. It demonstrated that higher pressures were associated with more pronounced respiratory and haemodynamic changes as well as increased post-operative pain scores and prolonged time to resume feeding.

3.23.2.3 Pulmonary effects

After intra-abdominal insufflation the diaphragm is pushed upwards due to increased abdominal pressure. This leads to decreased total pulmonary compliance. Combined with CO_2 absorption this may lead to hypercarbia and acidosis, particularly in case of prolonged operative time or low pulmonary reserve such as in infants. Trendelenburg position may also aggravate the situation in operations in the pelvic region, such as anti-reflux or bladder neck surgeries. Several studies revealed increased end tidal CO_2 (ET CO_2) related to CO_2 absorption [1430, 1435, 1436]. One study showed a 33% increase in ET CO_2 in the majority of neonatal laparoscopic and thoracoscopic procedures [1244]. Shorter operative time and lower intra-abdominal pressures decrease the risk of increased ET CO_2. Hypoxemia is rarely seen, even in neonates and can easily be adjusted by increasing minute ventilation. These findings highlight the importance of close monitoring of the children.

3.23.2.4 Cardiovascular effects

Intra-abdominal pressure, CO_2 absorption and positioning may also affect the cardiovascular system. It has been shown in adults that after initiation of pneumoperitoneum, cardiac output and stroke volume decrease while mean arterial pressure, central venous pressure and systemic vascular resistance increase [1437]. Similar outcomes have been reported during paediatric laparoscopy with some nuances. Cardiac output was 30% decreased while blood pressure remained stable during laparoscopic orchidopexy with PnP of 10 mmHg in children between aged 6-30 months [1438]. When PnP was lowered from 12 mmHg to 6 mmHg, cardiac index and other vascular parameters normalised [1439]. Using high intra-abdominal pressures in infants with congenital cardiac abnormalities may result in re-opening of cardiac shunts such as the foramen ovale and ductus arteriosus [1440]. Although cardiovascular effects of using high PnP are clinically measurable, they may not have a significant clinical impact on healthy children. However, it is clear that using lower pressures is safer especially in smaller children.

3.23.2.5 Effects on renal function

Although clinical studies in children are lacking, pneumoperitoneum may also have adverse effects on renal blood flow [1441]. High intra-abdominal pressures and reverse Trendelenburg position may cause decreased glomerular filtration rate and decreased urine output. One study has shown that 88% of infants and 14% of children more than one year old develop anuria within 45 minutes after initiation of PnP with 8 mmHg [1442]. However, urine output recovers with temporary polyuria after the operation. Although the clinical relevance of decreased urine output seems insignificant, it is important to monitor the fluid and electrolyte balance of the children during and after laparoscopic surgery.

3.23.2.6 Effects on neurological system

Another effect of pneumoperitoneum is increased intracranial pressure (ICP) which normalises after desufflation of the abdomen [1443]. Trendelenburg position, high PnP and hypoventilation are additional risk factors for increased ICP. Laparoscopy is therefore contraindicated in patients with intracranial space occupying lesions [1444]. Children with ventriculo-peritoneal shunts require precautions with regards to shunt drainage, however laparoscopy is not contraindicated [1445].

3.23.3 *Summary of evidence and recommendations for laparoscopy in children*

Summary of evidence	LE
Laparoscopy and robotic-assisted laparoscopic surgery can safely be performed in children	1
The general benefits of laparoscopy are decreased pain, shorter convalescence and better cosmetics compared to traditional open surgery.	1
Limitations to be considered are increased operative time, smaller working space with young age, cost, surgeon and anaesthesiologist experience.	1
Pneumoperitoneum may have physiological effects which require close monitoring during surgery and should be taken seriously.	2

Recommendations	Strength rating
Use lower intra-abdominal pressure (6-8 mmHg) during laparoscopic surgery in infants and smaller children.	Strong
Use open access for laparoscopy in infants and smaller children.	Strong
Monitor for laparoscopy-related cardiac, pulmonary and diuretic responses.	Strong

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5. CONFLICT OF INTEREST

All members of the Paediatric Urology Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This Guidelines document was developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/
References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Penile Cancer

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines on Penile Cancer provides up-to-date information on the diagnosis and management of penile squamous cell carcinoma (SCC).

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Penile Cancer Guidelines Panel consists of an international multi-disciplinary group of clinicians, including a pathologist and an oncologist. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of having penile cancer. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/penile-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, the most recent dating back to 2014 [1], as are a number of translations of all versions of the Penile Cancer Guidelines. All documents are available through the EAU website Uroweb: http://uroweb.org/guideline/penile-cancer/.

1.4 Publication history

The EAU Penile Cancer Guidelines were first published in 2000; the current publication presents a limited update of the 2017 print.

1.5 Summary of changes

Key changes for the 2018 print:

Chapter 3 - Epidemiology, aetiology and pathology. New information has been added on the various histological subtypes of penile carcinomas, risk factors and human papilloma virus (HPV) association.

New and changed recommendations can be found in sections:

3.4.8 Guidelines for the pathological assessment of tumour specimens

Recommendations	Strength rating
The pathological evaluation of penile carcinoma specimens must include an assessment of the human papilloma virus status.	Strong
The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype.	Strong
The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin.	Strong

4.2 Guidelines on staging and classification

Recommendation	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM stage and an assessment of tumour grade.	Strong

5.4 Guidelines for the diagnosis and staging of penile cancer

Recommendations	Strength rating
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	Strong

Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery.	Weak
Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients; • If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT.	Strong
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan.	Strong
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

6.2.6 ***Guidelines for treatment strategies for nodal metastases***

Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**Strength rating**
Radiotherapy Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong
	> T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	Strong
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.	Strong
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphade-nectomy in responders.	Weak
Pelvic Lymph nodes	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported	Strong
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	Strong
Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong

6.3.6 ***Guidelines for chemotherapy***

Recommendations	**Strength rating**
Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide).	Strong
Offer palliative chemotherapy to patients with systemic disease.	Weak

A systematic review (SR) was performed by the Panel on 'Risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy in node-positive penile cancer' [2]. Even though not fully published, the review findings support the information presented in Section 6.2.2.3 Adjuvant treatment.

This review was performed using standard Cochrane SR methodology: http://www.cochranelibrary.com/about/about-cochrane-systematic-reviews.html

2. METHODS

2.1 Data identification

For the 2018 Penile Cancer Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Penile Cancer Guidelines, was performed. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering the period between November 1st 2013 and September 20th 2016. All articles relating to penile cancer (n = 838) in the relevant literature databases were reviewed resulting in the inclusion of 29 new publication in this print.

Fully revised Guidelines were produced using the updated research base, together with several national and international guidelines on penile cancer (National Comprehensive Cancer Network [3], French Association of Urology [4] and the European Society of Medical Oncology [5]).

For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines [6, 7]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation which is represented by the words 'strong' or 'weak' [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Definition of penile cancer

Penile carcinoma is usually a SCC and there are several recognised subtypes of penile SCC with different clinical features and natural history (see Table 1). Penile SCC usually arises from the epithelium of the inner prepuce or the glans.

Table 1: Histological subtypes of penile carcinomas, their frequency and outcome

Subtype	Frequency (% of cases)	Prognosis
Common squamous cell carcinoma (SCC)	48-65	Depends on location, stage and grade
Basaloid carcinoma	4-10	Poor prognosis, frequently early inguinal nodal metastasis [10]
Warty carcinoma	7-10	Good prognosis, metastasis rare
Verrucous carcinoma	3-8	Good prognosis, no metastasis
Papillary carcinoma	5-15	Good prognosis, metastasis rare
Sarcomatoid carcinoma	1-3	Very poor prognosis, early vascular metastasis
Mixed carcinoma	9-10	Heterogeneous group
Pseudohyperplastic carcinoma	< 1	Foreskin, related to lichen sclerosus, good prognosis, metastasis not reported
Carcinoma cuniculatum	< 1	Variant of verrucous carcinoma, good prognosis, metastasis not reported
Pseudoglandular carcinoma	< 1	High-grade carcinoma, early metastasis, poor prognosis
Warty-basaloid carcinoma	9-14	Poor prognosis, high metastatic potential [11] (higher than in warty, lower than in basaloid SCC)

Adenosquamous carcinoma	< 1	Central and peri-meatal glans, high-grade carcinoma, high metastatic potential but low mortality
Mucoepidermoid carcinoma	< 1	Highly aggressive, poor prognosis
Clear cell variant of penile carcinoma	1-2	Exceedingly rare, associated with human papilloma virus, aggressive, early metastasis, poor prognosis, outcome is lesion-dependent, frequent lymphatic metastasis [12]

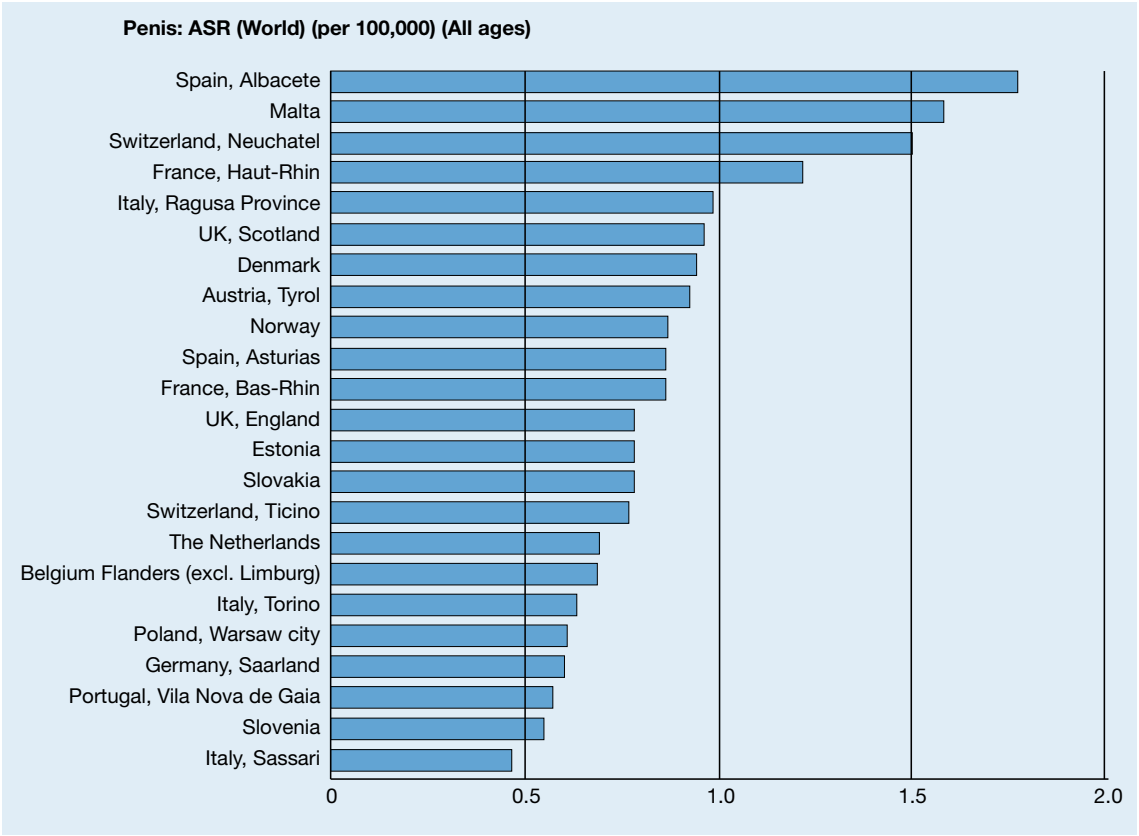
3.2 Epidemiology

In industrialised countries, penile cancer is uncommon, with an overall incidence of around 1/100,000 males in Europe and the USA [13, 14]. There are several areas in Europe with a higher incidence (Figure 1) [15]. Recent data from Scandinavia report an incidence of around 2/100,000 men. In the USA, the incidence of penile cancer is affected by race and ethnicity, with the highest incidence in white Hispanics (1.01), followed by Alaskans and Native American Indians (0.77), African Americans (0.62) and white non-Hispanics (0.51), per 100,000, respectively. In contrast, in some other parts of the world such as South America, South East Asia and parts of Africa the incidence is much higher and can account for 1-2% of malignant diseases in men [15]. The annual age-adjusted incidence is 0.7-3.0 in India, 8.3 in Brazil (per 100,000, respectively) and even higher in Uganda, where it is the most commonly diagnosed male cancer [15, 16].

In the USA, the overall age-adjusted incidence rate decreased from 1973 to 2002 from 0.84 in 1973-1982 to 0.69 in 1983-1992, and to 0.58 in 1993-2002, per 100,000, respectively [13]. In Europe, the overall incidence has been stable from the 1980s until 2013 [14]. An increased incidence was observed in Denmark [17] and the UK (21% between 1979 and 2009) [18].

The incidence of penile cancer increases with age [14], with a peak in the sixth decade but it does occur in younger men [19]. Penile cancer is common in regions with a high prevalence of HPV and this may account for the worldwide variation in incidence [13]. About one third of cases are attributed to HPV-related carcinogenesis [20]. Penile cancer is not linked to HIV or AIDS.

Figure 1: Annual incidence rate (world standardised) by European region/country*



Adapted from [15].

3.3 Risk factors and prevention

Several risk factors for penile cancer have been identified (Table 2) [21] (LE: 2a).

Table 1: Recognised aetiological and epidemiological risk factors for penile cancer

Risk factors	Relevance	Ref
Phimosis	Odds ratio 11-16 vs. no phimosis	[22-24]
Chronic penile inflammation (balanoposthitis related to phimosis), lichen sclerosus	Risk	[25]
Sporalene and ultraviolet A phototherapy for various dermatological conditions such as psoriasis	Incidence rate ratio 9.51 with > 250 treatments	[26]
Smoking	Five-fold increased risk (95% Confidence interval (CI): 2.0-10.1) vs. non-smokers	[22, 23, 27]
HPV infection, condylomata acuminate	22.4% in verrucous squamous cell carcinoma 36-66.3% in basaloid-warty	[13, 28]
Rural areas, low socio-economic status, unmarried		[29-32]
Multiple sexual partners, early age of first intercourse	Three to five-fold increased risk of penile cancer	[21, 23, 33]

Human papilloma virus infection is a risk factor for penile cancer [34]. Human papilloma virus DNA has been identified in 70-100% of intra-epithelial neoplasia and in 30-40% of invasive penile cancer tissue samples (LE: 2a). The HPV virus interacts with oncogenes and tumour suppressor genes (*p16, P53, Rb* genes) [28, 35]. The rate of HPV-positivity differs between different histological subtypes of penile SCC. Human papilloma virus is a cofactor in the carcinogenesis of some variants of penile SCC, while others are not related to HPV. The commonest HPV subtypes in penile cancer are types 16 and 18 [36]. The risk of penile cancer is increased in patients with condyloma acuminata [37] (LE: 2b).

A significantly better five-year disease-specific survival has been reported for HPV-positive vs. HPV-negative cases (93% vs. 78%) in one study [38], while no difference in lymph node metastases and ten-year survival was reported in another study [39] (Table 3). There is no association between the incidence of penile and cervical cancer, although both are linked to HPV [40, 41]. Female sexual partners of patients with penile cancer do not have an increased incidence of cervical cancer [42].

Table 3: Outcomes for HPV and non-HPV penile carcinomas

Non HPV related	Prognosis	HPV related	Prognosis
SCC usual type/NOS	30% DOD	Basaloid SCC	> 50% DOD
Pseudohyperplastic carcinoma	0%	Papillary basaloid carcinoma	
Pseudoglandular carcinoma	> 50%	Warty carcinoma	Mortality low
Verrucous carcinoma	Good	Warty-basaloid carcinoma	30% DOD
Carcinoma cuniculatum	Good	Clear-cell carcinoma	20%
Papillary carcinoma NOS	Good	Lymphoepithelioma-like carcinoma	Not known
Adenosquamous carcinoma	Good		
Sarcomatoid carcinoma	75% DOD		

DOD = died of disease; HPV = human papillomavirus; SCC = squamous cell carcinoma.

At present, except for a few countries, there is no general recommendation for HPV vaccination in males because of the different HPV-associated risk patterns in penile- and cervical cancer. Furthermore, the epidemiological effects of HPV vaccination in girls still have to be assessed [43, 44].

Phimosis is strongly associated with invasive penile cancer [23, 29, 45, 46], due to associated chronic infection. However, smegma is not a carcinogen [45]. The incidence of lichen sclerosus is relatively high in penile cancer but is not associated with adverse histopathological features, including penile intraepithelial neoplasia (PeIN). Other epidemiological risk factors are cigarette smoking, low socioeconomic status and a low level of education [29, 46].

Neonatal circumcision reduces the incidence of penile cancer; however, it does not seem to reduce the risk of PeIN [23]. The lowest incidence of penile cancer is reported for Israeli Jews (0.3/100,000/year). One matched-pair, case-control study reported that the protective effect of neonatal circumcision against invasive penile cancer (OR 0.41) was much weaker when the analysis was restricted to men without a history of phimosis (OR 0.79, 95% CI: 0.29-2) [23]. Circumcision in adult life does not have any protective effect.

The controversial discussion about neonatal circumcision should take into account that circumcision removes approximately half the tissue that can develop into penile cancer.

3.4 Pathology

Squamous cell carcinoma accounts for over 95% of penile malignancies (see Table 1). It is not known how often SCC is preceded by premalignant lesions (see Table 4) [47-50].

Different histological types of penile SCC with different growth patterns, clinical aggressiveness and HPV associations have been identified (see Table 5). Numerous mixed forms exist such as the warty-basaloid form, with 50-60% the most common mixed form, the usual-verrucous (hybrid), usual-warty, usual-basaloid and the usual-papillary, as well as other rarer combinations.

Other malignant lesions of the penis, all much less common than penile SCC, are melanocytic lesions, mesenchymal tumours, lymphomas and metastases. Penile metastases are frequently of prostatic or colorectal origin. Different types of penile sarcoma have been reported.

Table 4: Premalignant penile lesions (precursor lesions)

Lesions sporadically associated with squamous cell carcinoma (SCC) of the penis: • Bowenoid papulosis of the penis (HPV related) • Lichen sclerosis
Premalignant lesions (up to one-third transform to invasive SCC): • Penile intraepithelial lesions • Giant condylomata (Buschke-Löwenstein) • Bowen's disease • Paget's disease (intradermal ADK)

Table 5: Classification of intra-epithelial neoplasia (PeIN)

• **Non-HPV-related PeIN**
• o Differentiated PeIN
• **HPV-related PeIN**
• o Basaloid PeIN
• **Warty PeIN**
• **Warty-basaloid PeIN**
• **Other rare patterns of PeIN** (pleomorphic, spindle, clear cell, pagetoid)

3.4.1 Gross handling of pathology specimens

Tissue sections determine the accuracy of histological diagnosis. Small lesions should be fully included, bigger lesions should have at least 3-4 blocks. Lymph nodes must be included in their entirety after having been inked, in order to detect metastases. After having been inked, surgical margins have to be completely included [51]. Second-opinion pathology review is highly desirable for this rare tumour entity [52].

3.4.2 Pathology report

The pathology report must include the anatomical site of the primary tumour, the histological type of SCC, grade, perineural invasion, depth of invasion, vascular invasion (venous/lymphatic), irregular growth and front of invasion, urethral invasion, invasion of corpus spongiosum/cavernosum, surgical margins and the *p16*/HPV status (Table 6) [53-56].

Table 6: Outcomes for HPV and non-HPV penile carcinomas

Information to include in the pathology report	Recommended	required
Clinical information • Prior treatments (topic, radiotherapy, chemotherapy)	x	
Surgical procedure		x
Tumour localisation	x	
Macroscopic tumour dimension • Depth of invasion • Millimetres from basement membrane to deepest point of invasion • Maximum thickness • Size of tumour		x
Block identification	x	
Histological tumour type		x
Histological grade		x
Microscopic maximum dimensions • Combination of gross and microscopic if large tumours		x
Extent of invasion		x
LVI [58, 59]		x
Perineural invasion		x
Margin status in mm		x
Lymph node (LN) status • Size of largest nodal tumour deposit (not LN size) • Number of LN+, extracapsular spread (ECS), inguinal or pelvic, to be reported in every site separately		x
TNM Stage		x
p16/HPV status	x	

** See also www.ICCR-cancer.org. database.*

3.4.3 Grading

The TNM classification for penile cancer includes tumour grade, due to its prognostic relevance (Table 9). Tumour grading in penile cancer has been shown to be highly observer-dependent and can be problematic, especially in heterogeneous tumours. Grading should use the categories specified by the WHO for penile cancer (Table 7).

Table 7: Grading recommendations for penile SCC

Feature	Grade 1	Grade 2	Grade 3	Sarcomatoid
Cytological atypia	Mild	Moderate	Anaplasia	Sarcomatoid
Keratinisation	Usually abundant	Less prominent	May be present	Absent
Intercellular bridges	Prominent	Occasional	Few	Absent
Mitotic activity	Rare	Increased	Abundant	Abundant
Tumour margin	Pushing/well	Infiltrative/ill defined	Infiltrative/ill defined	Infiltrative/ill defined

3.4.4 Pathological prognostic factors

Pathological subtype, perineural invasion, lymphovascular invasion [58], depth of invasion and grade in the primary tumour are strong predictors of poor prognosis and high cancer-specific mortality [60]. Tumour grade is a predictor of metastatic spread, and lymphatic invasion is a predictor of metastasis. Venous embolism is often seen in advanced stages. The extent of lymph node metastasis and extracapsular spread are also strong predictors of prognosis.

The variants of penile SCC can be divided into three prognostically different groups (Table 8).

Table 8: Prognosis of the variants of penile SCC

Penile SCC	Good prognosis	Intermediate prognosis	Poor prognosis
Local growth	Destructive	Destructive	Destructive
Metastasis	Rare	Intermediate	Common
Risk of cancer-related mortality	Very low	Intermediate	High
SCC variants	• Verrucous • Papillary • Warty Pseudohyperplastic carcinoma cuniculatum	• Usual SCC • Mixed forms • Pleomorphic form of warty carcinoma	• Basaloid, • Sarcomatoid adenosquamous

There is discussion as to whether cases that show invasion of the distal urethra have a worse prognosis; however, there is no evidence to support this [61]. Nevertheless, invasion of the more proximal urethra signifies a highly aggressive SCC with a poor prognosis (see Table 9). pT3 denotes a worse prognosis than pT2 [62, 63] (LE: 2b). Capsular extension in even one single lymph node carries a poor prognosis and is denoted as pN3 [64-66].

Chaux *et al.* suggested a prognostic index which incorporates grade, anatomical level of infiltration and perineural invasion to predict the likelihood of inguinal lymph node metastases and 5-year survival [67].

3.4.5 Penile cancer and HPV

The association between penile cancer and HPV is different for the different variants of penile SCC. A high prevalence of HPV infection is found in basaloid (76%), mixed warty-basaloid (82%) and warty penile (39%) SCCs. Verrucous and papillary penile SCCs are HPV-negative. The commonest HPV-types in penile SCC are HPV-16 (72%), HPV-6 (9%) and HPV-18 (6%). Overall, only one-third of penile SCCs show HPV infection, but those that do are usually infected by several HPV strains.

3.4.6 Penile biopsy

Any doubtful penile lesion should be biopsied and, even in clinically obvious cases, histological verification must be obtained before local treatment. Before definitive surgical treatment, confirmatory frozen section excisional biopsy can be done. Histological confirmation is necessary to guide management when:

- there is doubt about the exact nature of the lesion (e.g. PeIN, metastasis or melanoma);
- treatment is planned with topical agents, radiotherapy or laser surgery.

The size of a biopsy is important. In one study, in biopsies with an average size of 0.1 cm it was difficult to evaluate the depth of invasion in 91% of cases. The grade at biopsy, and in the final specimen, may differ in up to 30% of cases, with failure to detect cancer in 3.5% of cases [47]. Furthermore, vascular and lymphatic tumour emboli were detected in only 9-11% of cases. Although a punch biopsy may be sufficient for superficial lesions, an excisional biopsy which is deep enough to properly assess the degree of invasion and stage is preferable.

3.4.7 Intra-operative frozen sections and surgical margins

Surgical treatment must completely remove the penile carcinoma with negative surgical margins, which may be confirmed by intra-operative frozen section [68]. The width of negative surgical margins should follow a risk-adapted strategy based on tumour grade. Only 3 mm of tumour-free tissue is sufficient to consider the surgical margins to be negative [69].

3.4.8 Guidelines for the pathological assessment of tumour specimens

Recommendations	Strength rating
The pathological evaluation of penile carcinoma specimens must include an assessment of the human papilloma virus status.	Strong
The pathological evaluation of penile carcinoma specimens must include a diagnosis of the squamous cell carcinoma subtype.	Strong
The pathological evaluation of penile carcinoma surgical specimens must include an assessment of surgical margins including the width of the surgical margin.	Strong

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 TNM classification

The 2016 UICC TNM classification for penile cancer [51] introduced some changes in comparison to previous editions. The T1 category is stratified into two prognostically different risk groups, depending on the presence or absence of lymphovascular invasion and grading (Table 9). The classification T2 denotes invasion of the corpus spongiosum, while T3 is defined as invasion of the corpora cavernosa, due to the different prognosis of these two patterns [62, 63]. For penile cancer, unlike in other neoplasms, tumour grade is used for the TNM classification in the subdivision of the T1 stage (Table 9).

The current pN1 group consists of one or two ipsilateral inguinal lymph node metastases, pN2 is defined as more than two uni- or bilateral metastatic nodes and pN3 any pelvic nodes, uni- or bilateral, or any extranodal extension regardless of the number of lymph node metastases [51]. Retroperitoneal lymph node metastases are classified as extra-regional nodal and, therefore, distant metastases.

Table 9: 2016 TNM clinical and pathological classification of penile cancer [51]

Clinical classification	
T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma*
T1	Tumour invades subepithelial connective tissue
T1a	Tumour invades subepithelial connective tissue without lymphovascular invasion and is not poorly differentiated
T1b	Tumour invades subepithelial connective tissue with lymphovascular invasion or is poorly differentiated
T2	Tumour invades corpus spongiosum with or without invasion of the urethra
T3	Tumour invades corpus cavernosum with or without invasion of the urethra
T4	Tumour invades other adjacent structures
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No palpable or visibly enlarged inguinal lymph nodes
N1	Palpable mobile unilateral inguinal lymph node
N2	Palpable mobile multiple or bilateral inguinal lymph nodes
N3	Fixed inguinal nodal mass *or* pelvic lymphadenopathy, unilateral or bilateral
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Pathological classification	
The pT categories correspond to the clinical T categories. The pN categories are based upon biopsy or surgical excision	
pN - Regional Lymph Nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in one or two inguinal lymph nodes
pN2	Metastasis in more than two unilateral inguinal nodes or bilateral inguinal lymph nodes
pN3	Metastasis in pelvic lymph node(s), unilateral *or* bilateral extranodal or extension of regional lymph node metastasis
pM - Distant Metastasis	
pM1	Distant metastasis microscopically confirmed
G - Histopathological Grading	
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

**Verrucous carcinoma not associated with destructive invasion.*

4.2 Guidelines on staging and classification

Recommendation	Strength rating
The pathological evaluation of penile carcinoma specimens must include the pTNM stage and an assessment of tumour grade.	Strong

5. DIAGNOSTIC EVALUATION AND STAGING

Penile cancer can be cured in over 80% of cases if diagnosed early, but is a life-threatening disease when lymphatic metastasis occurs. Local treatment can be mutilating, and devastating for the patient's psychological well-being.

5.1 Primary lesion

Penile carcinoma is usually a clinically obvious lesion but it may be hidden under a phimosis [24]. Physical examination should include palpation of the penis to assess the extent of local invasion and palpation of both groins to assess the lymph node status.

Ultrasound (US) can provide information about infiltration of the corpora [70, 71]. Magnetic resonance imaging (MRI) with an artificially induced erection can be used to exclude corporal invasion but is very unpleasant for the patient [72, 73]. The sensitivity and specificity of MRI in predicting corporal or urethral invasion was reported as 82.1% and 73.6%, and 62.5% and 82.1%, respectively [74]. Penile Doppler US has been reported to have a higher staging accuracy than an MRI in detecting corporal infiltration [75].

5.2 Regional lymph nodes

Careful palpation of both groins for enlarged inguinal lymph nodes must be part of the initial physical examination of patients suspected of having penile cancer.

5.2.1 Non-palpable inguinal nodes

If there are no palpable lymph nodes, the likelihood of micro-metastatic disease is about 25%. Imaging studies are not helpful in staging clinically normal inguinal regions, although may be used in obese patients in whom palpation is unreliable:

- Inguinal US (7.5 MHz) can detect abnormal, enlarged nodes. The longitudinal/transverse diameter ratio and absence of the lymph node hilum are findings with relatively high specificity [76].
- Conventional computed tomography (CT) or MRI cannot detect micro-metastases reliably [77].
- ^{18}FDG-positron emission tomography (PET/CT) does not detect lymph node metastases < 10 mm [78, 79].

Further management of patients with normal inguinal nodes should be guided by pathological risk factors of the primary tumour. Lymphovascular invasion, local stage and grade are predictive of lymphatic metastasis [80, 81]. Existing nomograms are not accurate. Invasive lymph node staging is required in patients at intermediate- or high risk of lymphatic spread (see Section 6.2).

5.2.2 Palpable inguinal nodes

Palpably enlarged lymph nodes are highly indicative of lymph node metastases. Physical examination should note the number of palpable nodes on each side and whether these are fixed or mobile. Additional imaging does not alter management and is not required (see Section 6).

A pelvic CT scan can be used to assess the pelvic lymph nodes. Imaging with ^{18}FDG-PET/CT has shown high sensitivity (88-100%) and specificity (98-100%) for confirming metastatic nodes in patients with palpable inguinal lymph nodes [79, 82].

5.3 Distant metastases

Staging for systemic metastases should be performed in patients with positive inguinal nodes [83-85] (LE: 2b). Abdominal and pelvic CT should be done plus a chest X-ray, although a thoracic CT is more sensitive. PET/CT is an option [81].

There is no tumour marker for penile cancer. The SCC antigen (SCC Ag) is increased in less than 25% of penile cancer patients. One study reported that SCC Ag did not predict occult metastatic disease, but was an indicator of disease-free survival (DFS) in lymph-node-positive patients [86].

5.4 Guidelines for the diagnosis and staging of penile cancer

Recommendations	Strength rating
Primary tumour	
Perform a physical examination, record morphology, extent and invasion of penile structures.	Strong
Obtain a penile Doppler ultrasound or MRI with artificial erection in cases with intended organ-sparing surgery.	Weak
Inguinal lymph nodes	
Perform a physical examination of both groins, record the number, laterality and characteristics of inguinal nodes and: • If nodes are not palpable, offer invasive lymph node staging in intermediate- and high-risk patients; • If nodes are palpable, stage with a pelvic computed tomography (CT) or positron emission tomography (PET)/CT.	Strong
Distant metastases	
In N+ patients, obtain an abdominopelvic CT scan and chest X-ray/thoracic CT for systemic staging. Alternatively, stage with a PET/CT scan.	Strong
In patients with systemic disease or with relevant symptoms, obtain a bone scan.	

6. DISEASE MANAGEMENT

6.1 Treatment of the primary tumour

The aims of the treatment of the primary tumour are complete tumour removal with as much organ preservation as possible, without compromising oncological control. Local recurrence has little influence on long-term survival, so organ preservation strategies are justified [87].

There are no randomised controlled trials (RCTs) or observational comparative studies for any of the treatment options for localised penile cancer. Penile preservation appears to be superior in functional and cosmetic outcomes to partial or total penectomy, and is considered to be the primary treatment method for localised penile cancer. However, there are no RCTs comparing organ-preserving and ablative treatment strategies.

Histological diagnosis with local staging must be obtained before using non-surgical treatments. With surgical treatment, negative surgical margins must be obtained. Treatment of the primary tumour and of the regional nodes can be staged.

Local treatment modalities for small and localised penile cancer include excisional surgery, external beam radiotherapy (EBRT), brachytherapy and laser ablation. Patients should be counselled about all relevant treatment options.

6.1.1 Treatment of superficial non-invasive disease (PeIN)

Topical chemotherapy with imiquimod or 5-fluorouracil (5-FU) is an effective first-line treatment. Circumcision is advisable prior to the use of topical agents. Due to high persistence/recurrence rates, treatment must be assessed by biopsy and long-term surveillance is warranted. An insufficient response may signify underlying invasive disease. Significant inflammatory responses may occur [88, 89]. Complete responses have been reported in up to 57% of PeIN cases [90] and in 74% of cases treated by circumcision and 5-FU without relapse. If topical treatment fails, it should not be repeated.

Laser treatment with a neodymium:yttrium-aluminium-garnet (Nd:YAG) or Carbon dioxide (CO_2) laser is an effective treatment option [91-96]. Visualisation may be improved by photodynamic diagnosis with the CO_2 laser [97]. Rebiopsy for treatment control is mandatory.

Glans resurfacing, total or partial, can be a primary treatment for PeIN or a secondary option in case of failure of topical chemotherapy or laser therapy. Glans resurfacing consists of complete removal of the glandular epithelium followed by reconstruction with a graft (split skin or buccal mucosa). However, in one study in cases of glans resurfacing for presumed PeIN, up to 20% of patients were found to have invasive disease on histopathological examination [88].

6.1.2 *Treatment of invasive disease confined to the glans (category T1/T2)*

Small and localised invasive lesions should receive organ-sparing treatment. Additional circumcision is advisable for glandular tumours. Foreskin tumours are treated by 'radical circumcision'. Local excision, partial glansectomy or total glansectomy with reconstruction are surgical options. External beam radiotherapy or brachytherapy are radiotherapeutic options. Small lesions can also be treated by laser therapy but the risk of more invasive disease must be recognised.

Treatment choice depends on tumour size, histology, stage and grade, localisation (especially relative to the meatus) and patient preference.

6.1.2.1 *Intra-operative frozen section*

Many authors recommend intraoperative frozen sections to assess surgical margins. Others have suggested that frozen sections are only needed if there are definite concerns [98]. For glans resurfacing, some advocate the use of acetic acid staining to delineate abnormal areas [99]. Data from one multi-centre study suggests that differentiated penile intraepithelial neoplasia, squamous hyperplasia and lichen sclerosis present at the surgical margins are frequent findings and are not relevant for cancer-specific survival [65].

6.1.2.2 *Width of negative surgical margins*

There is no clear evidence as to the required width of negative surgical margins. With organ-sparing these can be minimal. For a general recommendation, 3-5 mm can be considered a safe maximum [100, 101]. A grade-based differentiated approach can also be used, with 3 mm for grade one, 5 mm for grade two and 8 mm for grade three. This approach has its limitations due to the difficulties with penile cancer grading.

6.1.3 *Results of different surgical organ-preserving treatments*

6.1.3.1 *Laser therapy*

The results of CO_2 laser treatment have been reported by three retrospective studies from the same institution with a median follow-up of five years and a total of 195 patients [91-93]. Laser treatment was given in combination with radiotherapy or chemotherapy for PeIN or T1 penile cancers. No cancer-specific deaths were reported. Local recurrence ranged from 14% for PeIN [93] to 23% for T1 tumours [92], with an estimated cumulative risk of local recurrence at five years of 10% for PeIN (n = 106) and 16% for T1 (n = 78) tumours [91]. The reported rate of inguinal nodal recurrence was between 0% [93] and 4% [92]. The rate of secondary partial penectomy at ten years was 3% for PeIN and 10% for T1 tumours [91].

Four studies, three from the same institution, reported results of Nd:YAG laser treatment for a total of 150 patients with a follow-up of at least four years [94-96, 102]. Local recurrence rates ranged from 10% to 48% [94, 95]. One study [96] reported recurrence-free survival rates of 100%, 95% and 89% at one, two and five years, respectively. Inguinal nodal recurrence was reported in 21% of patients [94] and cancer-specific mortality was reported as 2% [102] and 9% [95]. The three studies from the same institution reported overall survival (OS) rates of 100% at four years [94] and 85-95% [96, 103] at seven years. The rate of secondary partial penectomy was highly divergent, with 4% in one study [96] and 45% in another [95]. One study reported that no complications and no adverse effects on urinary or sexual function were observed [94].

Other studies have presented data on a variety of laser treatments with either a CO_2 or a Nd:YAG laser, a combination of both, or a potassium titanyl phosphate (KTP) laser [104-107], with a mean follow-up of 32-60 months with stages PeIN to T3 included. These studies reported on a total of 138 patients, with local recurrence rates of 11% [92], 19% [105] and 26% [107]. In one study, recurrence-free survival at five years was 88% [105]. The cancer-specific survival (CSS) probability at five years was 95% in one study [105], and 2% at five years in another [105].

6.1.3.2 *Moh's micrographic surgery*

Moh's micrographic surgery is a historical technique by which histological margins are taken in a geometrical fashion around a conus of excision. The original description [108] consisted of 33 consecutive patients treated between 1936 and 1986 with 79% cured at five years [108]. The second study reported 68% recurrence-free survival at three years, 32% local recurrences and 8% inguinal nodal recurrence [109]. In both studies, one partial amputation and one cancer-specific death occurred. In a contemporary series of 48 cases, there were no recurrences among 10 primary invasive SCCs with a cure rate of 100% (mean follow-up, 161 months, median follow-up, 177 months), but one recurrence in 19 cases of penile intraepithelial neoplasia (cure rate 94.7%) [110].

6.1.3.3 *Glans resurfacing*

Three studies have reported results of glans resurfacing in a total of 71 patients with PeIN or T1 with a median follow-up of 21-30 months [88, 111, 112]. No cancer-specific deaths were reported, the rates of local recurrence were 0% [111] and 6% [112], without reports of nodal recurrence or complications.

6.1.3.4 ***Glansectomy***

Results of glansectomy were reported in three studies [100, 113, 114], while a fourth also reported on glans-preserving surgery [114]. One study reported 87 patients with six local (6.9%), eleven regional (12.6%) and two systemic recurrences (2.3%) with a mean follow-up of 42 months [100]. The other two studies reported on a total of 68 patients with a follow-up of 63 [114] and 114 months [113], respectively, in which there was one patient (8%) with local recurrence [113], six (9%) with inguinal nodal recurrence, and no cancer-specific deaths.

6.1.3.5 ***Partial penectomy***

Results of partial penectomy were reported in rather heterogeneous studies with a total of 184 patients with T1-T3 tumours and a follow-up of 40-194 months [93, 114-119]. The rate of local recurrence ranged from 4-50% and cancer-specific mortality from 0-27%. The reported five-year OS ranged from 59-89% [117, 119, 120].

6.1.3.6 ***Summary of results of surgical techniques***

Although conservative, organ-sparing surgery may improve quality of life (QoL), local recurrence is more likely than after amputation surgery for penile cancer. In one study the local recurrence rate after organ-sparing surgery was 18%, most of these occurred within 36 months [121], and amputation was necessary in 17% of the recurrences. Compared to this, the local recurrence rate after amputation surgery (partial or radical) was lower (4%). Glansectomy with circumcision for the treatment of small penile lesions has a very low rate of local recurrence (2%) [100].

In one large cohort of patients undergoing organ-sparing surgery, isolated local recurrence was 8.9% and five-year disease-specific survival (DSS) 91.7%. Tumour grade, stage and lymphovascular invasion were predictors of local recurrence. In the largest cohort of penile surgery, the 5-year cumulative incidence of local recurrence after organ-sparing (including laser treatment) was 27% while it was only 3.8% in the amputation group [98]. Of the 451 patients treated by organ-sparing surgery, 16% eventually underwent amputation. However, there was no significant difference in survival between the organ-sparing and the amputation groups. These results suggest that the local recurrence rates following penile preserving surgery are higher than with partial penectomy, although survival appears to be unaffected.

6.1.4 ***Summary of results of radiotherapy for T1 and T2 disease***

Radiotherapy is an organ-preserving approach with good results in selected patients with T1-2 lesions < 4 cm in diameter [122-127] (LE: 2b). It can be given as external radiotherapy with a minimum dose of 60 Gy combined with a brachytherapy boost or as brachytherapy alone [123, 125]. Reported results are best with brachytherapy with local control rates ranging from 70-90% [123, 125]. The American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society of Therapeutic Radiation Oncology consensus statement for penile brachytherapy also reported good tumour control rates, acceptable morbidity and functional organ preservation for penile brachytherapy for stages T1 and T2 [128]. Penile preservation rates of 70-88% have been reported [129], with overall penile conservation rates of 87% and 70% at five and ten years. Pulsed-dose-rate brachytherapy has been introduced as a new modality and 15% local recurrences have been reported in one series [130].

In the few comparisons of surgical treatment and radiotherapy, results of surgery were slightly better. In a meta-analysis comparing surgery and brachytherapy, 5-year OS and local control rates with surgery were 76%/84% for surgery and 73%/79% for brachytherapy, respectively [131]. The organ preservation rate for brachytherapy was 74% and there was no difference in survival. Local recurrence after radiotherapy can be salvaged by surgery [132].

Specific complications of radiotherapy for penile cancer are urethral stenosis (20-35%), glans necrosis (10-20%) and late fibrosis of the corpora cavernosa [133] (LE: 3). With brachytherapy, meatal stenosis has been reported to occur in 40% of cases, but was much lower in a contemporary series of 73 patients with only 6.6%. In that series, 2.6% reported pain with sexual intercourse and 5.3% dysuria over a follow-up of 5 years. Penile amputation for necrosis was necessary in 6.8 % of patients [134].

Functional outcome after radiotherapy has not often been reported. In one report, 17/18 patients with normal erections before treatment maintained these after treatment [129].

Table 10 provides an overview of the complications and outcomes of primary local treatments.

Table 10: Summary of reported complications and oncological outcomes of local treatments*

Treatment	Complications	Local recurrence	Nodal recurrence	Cancer-specific deaths	References
ND:YAG laser	n.r.	10-48%	21%	2-9%	[94-96, 102]
C02 laser	Bleeding, meatal stenosis, both < 1%	14-23%	2-4%	n.r.	[91-93]
Lasers (unspecified)	Bleeding 8%, local infection 2%	11-26%	2%	2-3%	[104-107]
Moh's micrographic surgery	Local infection 3%, Meatal stenosis 6%	32%	8%	3-4%	[108-110]
Glans resurfacing	n.r.	4-6%	n.r.	n.r.	[88, 111, 112, 135]
Glansectomy	n.r.	8%	9%	n.r.	[113, 114]
Partial penectomy	n.r.	4-13%	14-19%	11-27%	[93, 117, 119, 120]
Brachytherapy	Meatal stenosis > 40%	10-30%	n.r.	n.r.	[122, 123, 125]
External beam radiotherapy	Urethral stenosis 20-35%, Glans necrosis 10-20%	n.r.	n.r.	n.r.	[123, 127, 128, 132, 133]

**The ranges are the lowest and highest number of occurrences reported in different series.*

*6.1.5 **Treatment recommendations for invasive penile cancer (T2-T4)***

6.1.5.1 Treatment of invasive disease confined to the glans with or without urethral involvement (T2)

Total glansectomy, with or without resurfacing of the corporeal heads, is recommended [115] (LE: 3). Radiotherapy is an option (see Section 6.1.6). Partial amputation should be considered in patients unfit for reconstructive surgery [132].

6.1.5.2 Treatment of disease invading the corpora cavernosa and/or urethra (T3)

Glansectomy with distal corporectomy and reconstruction or partial amputation with reconstruction are standard [100, 101, 126]. Radiation therapy is an option.

6.1.5.3 Treatment of locally advanced disease invading adjacent structures (T4)

Extensive partial amputation or total penectomy with perineal urethrostomy is the standard advisable treatment [101]. For locally advanced and ulcerated cases, neoadjuvant chemotherapy may be an option. Otherwise, adjuvant chemotherapy or palliative radiotherapy are options (see Sections 6.2.4 and 6.1.6).

6.1.5.4 Local recurrence after organ-conserving surgery

A second organ-conserving procedure can be performed if there is no corpus cavernosum invasion [97, 101, 121, 126, 136]. For large or high-stage recurrence, partial or total amputation is required [133]. A total phallic reconstruction may be offered to patients undergoing total/subtotal amputation [137, 138].

*6.1.6 **Guidelines for stage-dependent local treatment of penile carcinoma***

Primary tumour	Use organ-preserving treatment whenever possible	Strength rating
Tis	Topical treatment with 5-fluorouracil (5-FU) or imiquimod for superficial lesions with or without photodynamic control.	Strong
	Laser ablation with carbon dioxide (CO_2) or neodymium:yttrium-aluminium-garnet (Nd:YAG) laser.	
	Glans resurfacing.	
Ta, T1a (G1, G2)	Wide local excision with circumcision, CO_2 or Nd:YAG laser with circumcision.	Strong
	Laser ablation with CO_2 or Nd:YAG laser.	
	Glans resurfacing.	
	Glansectomy with reconstruction.	
	Radiotherapy for lesions < 4 cm.	

T1b (G3) and T2	Wide local excision plus reconstruction.	Strong
	Glansectomy with circumcision and reconstruction.	
	Radiotherapy for lesions < 4 cm in diameter.	
T3	Partial amputation with reconstruction or radiotherapy for lesions < 4 cm in diameter.	Strong
T3 with invasion of the urethra	Partial penectomy or total penectomy with perineal urethrostomy.	Strong
T4	Neoadjuvant chemotherapy followed by surgery in responders or palliative radiotherapy.	Weak
Local recurrence	Salvage surgery with penis-sparing in small recurrences or partial amputation.	Weak
	Large or high-stage recurrence: partial or total amputation.	

6.2 Management of regional lymph nodes

The development of lymphatic metastases in penile cancer follows the route of anatomical drainage. The inguinal lymph nodes, followed by the pelvic lymph nodes, provide the regional drainage system of penis. The superficial and deep inguinal lymph nodes are the first regional node group to be affected, which can be uni- or bilateral [87].

The 'sentinel' inguinal nodes, i.e. those first affected by lymphatic spread, appear to be located in the medial superior zone followed by the central inguinal zones [90]. No solitary lymphatic spread has been observed from the penis to the two inferior groin regions and no direct drainage to the pelvic nodes, either [88, 97]. These findings confirm earlier studies.

Pelvic nodal disease does not occur without ipsilateral inguinal lymph node metastasis. Also, crossover metastatic spread, from one groin to the contralateral pelvis, has never been reported. Further lymphatic spread from the pelvic nodes to retroperitoneal nodes (para-aortic, para-caval) is classified as systemic metastatic disease.

The management of regional lymph nodes is decisive for patient survival. Cure can be achieved in limited lymph node disease confined to the regional lymph nodes. Radical lymphadenectomy is the treatment of choice. Multimodal treatment combining surgery and chemotherapy is often indicated.

The management of regional lymph nodes is dependent on the clinical inguinal lymph node status. There are three possible scenarios. First, the clinical lymph nodes appear normal on palpation and are not enlarged. Secondly, the inguinal lymph nodes are palpably enlarged, either uni- or bilaterally. Thirdly, there are grossly enlarged and sometimes ulcerated inguinal lymph nodes, uni- or bilaterally.

In clinically node-negative patients (cN0), micro-metastatic disease occurs in up to 25% of cases and invasive lymph node staging is required since no imaging technique can reliably detect or exclude micro-metastatic disease. In clinically positive lymph nodes (cN1/cN2), metastatic disease is highly likely and lymph node surgery with histology is required. Enlarged fixed inguinal lymph nodes (cN3) require multimodal treatment by (neoadjuvant) chemotherapy and surgery. Even if present in only one node, capsular penetration/extra-nodal extension in lymph node metastasis carries a high risk of progression and is classified as pN3, which also requires multimodal treatment.

*6.2.1 **Management of patients with clinically normal inguinal lymph nodes (cN0)***

Risk stratification for the micro-metastatic inguinal lymph node disease depends on stage, grade and the presence/absence of lymphovascular invasion in the primary tumour [100]. pTa/pTis tumours and those with low grade have a comparatively low risk of lymphatic spread. Well-differentiated G1 pT1 tumours are considered low risk, pT1G2 intermediate risk and pT1G3 and all higher stage tumours are considered high risk for lymphatic spread [101].

For these patients, three management strategies are possible: surveillance, invasive nodal staging or radical lymphadenectomy. Early inguinal lymphadenectomy in clinically node-negative patients is superior for long-term patient survival compared to later lymphadenectomy with regional nodal recurrence [91, 92]. One prospective study comparing bilateral lymphadenectomy, radiotherapy and surveillance in such patients reported significantly better five-year OS lymphadenectomy vs. inguinal radiotherapy or surveillance (74% vs. 66% and 63%, respectively) [93].

6.2.1.1 Surveillance

Surveillance of regional lymph nodes carries the risk of regional recurrence arising later from existing micro-metastatic disease. Patient survival is over 90% with early lymphadenectomy and below 40% with lymphadenectomy for regional recurrence [94, 95]. Patients considering surveillance must be informed about this risk. Surveillance is only recommended in patients with pTis/pTa tumours and with the appropriate caveats in low risk G1 pT1 tumours [94-96]. Compliance is required for surveillance.

6.2.1.2 *Invasive nodal staging*

Since no imaging technique can detect micro-metastatic disease, invasive lymph node staging is recommended for pT1 tumours of intermediate and high risk, as well as for T2-T4 tumours [92, 105] (LE: 2b). Fine-needle aspiration cytology also does not reliably exclude micro-metastatic disease and is not recommended.

Invasive nodal staging can be done by either dynamic sentinel-node biopsy (DSNB) or by modified inguinal lymphadenectomy (mILND), both of which are standard techniques [139]. Dynamic sentinel-node biopsy aims to detect affected sentinel nodes in both groins. Technetium-99m (^{99m}Tc) nanocolloid is injected around the penile cancer site on the day before surgery often combined with patent blue. A gamma-ray probe is used intra-operatively to detect the sentinel nodes, which is possible in 97% of cases. The protocol has been standardised for routine use [107]. Dynamic sentinel-node biopsy has a reported high sensitivity in some centres (90-94%) [107, 108] (LE: 2b). In a meta-analysis of eighteen studies, the pooled sensitivity was 88%, which improved to 90% with the addition of patent blue [109].

Modified ILND is an alternative option, whereby the medial superficial inguinal lymph nodes and those from the central zone are removed bilaterally [87, 106] (LE: 3), leaving the greater saphenous vein untouched.

Both methods of invasive lymph node staging may miss micro-metastatic disease leading to regional recurrence [91]. The false-negative rate may be as high as 12-15% for DSNB, even in experienced centres [95, 96]. The false-negative rate of mILND is unknown. If lymph node metastasis is found, ipsilateral radical inguinal lymphadenectomy is indicated.

6.2.2 ***Management of patients with palpable inguinal nodes (cN1/cN2)***

With uni- or bilateral palpable inguinal lymph nodes (cN1/cN2), metastatic lymph node disease is highly likely. The notion that these may be inflammatory and that antibiotic treatment should first be used is unfounded and dangerous as it delays curative treatment.

Palpably enlarged groin lymph nodes should be surgically removed, pathologically assessed (by frozen section) and, if positive, a radical inguinal lymphadenectomy should be performed. In clinically doubtful cases, US-guided fine needle aspiration cytology is an option [140].

In such cases, CT or MRI can provide staging information about the pelvic nodal status and ^{18}F-FDGPET/CT can identify additional metastases [141]. Dynamic sentinel-node biopsy is not indicated in patients with palpably enlarged lymph nodes [142] (LE: 3).

6.2.2.1 *Radical inguinal lymphadenectomy*

Radical inguinal lymphadenectomy carries a significant morbidity due to impaired lymph drainage from the legs and scrotum. Morbidity can be as high as 50% [143] in the presence of significant risk factors such as increased body mass index (BMI). Recent series have reported lower morbidity in about 25% of cases [144, 145] (LE: 2b). Therapeutic radical inguinal lymphadenectomy can be life-saving and should not be underused for fear of associated morbidity [146].

Tissue handling must be meticulous in order to minimise post-operative morbidity. Lymphatic vessel walls do not contain smooth muscle and are therefore not reliably closed by electrocautery. Numerous metal clips may also cause post-operative problems so that ligation of all lymphatic vessels is advisable [147, 148]. Post-operative morbidity may be reduced by preserving the saphenous vein and post-operative measures to improve drainage, such as stockings, bandaging, inguinal pressure dressings or vacuum suction and prophylactic antibiotics [149]. Transposition of the Sartorius muscle is not recommended. There is no benefit from using fibrin glue intraoperatively [150]. Advanced cases may require reconstructive surgery for wound closure. The most commonly reported complications in recent series were wound infections (1.2-1.4%), skin necrosis (0.6-4.7%), lymphoedema (5-13.9%) and lymphocele formation (2.1-4%) [144, 145].

Minimally-invasive surgical techniques (laparoscopic, robot-assisted) for inguinal lymphadenectomy are technically feasible and, in small series, have been reported to significantly reduce post-operative morbidity except for the rate of lymphoceles [144, 150-153].

6.2.2.2 *Pelvic lymphadenectomy*

Patients with two or more inguinal lymph node metastases on one side and/or extracapsular lymph node extension need to undergo ipsilateral pelvic lymphadenectomy. This recommendation is based on a study in which the rate of positive pelvic nodes was found to be 23% in cases with more than two positive inguinal nodes and 56% in those with more than three positive inguinal nodes or extracapsular extension [101, 154] (LE: 2b).

Positive pelvic nodes carry a worse prognosis than only inguinal nodal metastasis (five-year CSS 71.0% vs. 33.2%) [155]. In a study of 142 groin node-positive patients, significant risk factors for pelvic nodal metastasis were the number of positive inguinal nodes (cut-off three), the diameter of inguinal metastatic nodes (cut-off 30 mm) and extra-nodal extension. The percentage of pelvic nodal metastases was 0% without any of these risk factors and 57.1% with all three risk factors present [155].

Pelvic lymphadenectomy may be performed simultaneously with inguinal lymphadenectomy or as a secondary procedure. If bilateral pelvic dissection is indicated, it can be performed through a midline suprapubic extraperitoneal incision. It is important to avoid unnecessary delay if these procedures are indicated [156].

6.2.2.3 Adjuvant treatment

In patients with pN2/pN3 disease, adjuvant chemotherapy is recommended after lymphadenectomy [157] (see Section 6.3.1). One retrospective study reported long-term DFS of 84% in node-positive patients with adjuvant chemotherapy after radical lymph node surgery vs. 39% in historical controls without adjuvant chemotherapy after lymphadenectomy [157]. More recent studies have confirmed the survival benefit of adjuvant chemotherapy after radical inguinal lymphadenectomy [158-160].

Although adjuvant radiotherapy has been used after inguinal lymphadenectomy, there are no data showing definite patient benefit. Adjuvant radiotherapy after inguinal lymphadenectomy should not be administered outside of clinical studies.

*6.2.3 **Management of patients with fixed inguinal nodes (cN3)***

Patients with large and bulky, sometimes ulcerated, inguinal lymph nodes require staging by thoracic, abdominal and pelvic CT for pelvic nodes and systemic disease. In clinically unequivocal cases, histological verification by biopsy is not required.

These patients have a poor prognosis. Multimodal treatment with neoadjuvant chemotherapy followed by radical lymphadenectomy in responders is recommended [161-163]. Responders to neoadjuvant chemotherapy with post-chemotherapy surgery have been reported to achieve long-term survival in 37% of cases [161]. Contemporary studies have confirmed this patient benefit [162, 164, 165].

*6.2.4 **Management of lymph node recurrence***

Patients with regional recurrence should be treated in the same way as patients with primary cN1/cN2 disease. However, patients with regional lymph node recurrence after DSNB or modified inguinal lymphadenectomy already have disordered inguinal lymphatic drainage and are at a high risk of irregular metastatic progression. Inguinal nodal recurrence after radical inguinal lymphadenectomy has a five-year CSS rate of 16% [166].

There is no evidence for the best management in such cases. Multimodal treatment with neoadjuvant and/or adjuvant chemotherapy after radical lymph node surgery is recommended.

*6.2.5 **The role of radiotherapy in lymph node disease***

Radiotherapy is used in some institutions for the treatment of inguinal lymph nodes. However, this is not evidence-based. One of the rare prospective trials in penile cancer found that inguinal radical lymphadenectomy is superior to inguinal radiotherapy for lymph-node positive penile cancer patients [167].

There is no evidence that adjuvant radiotherapy after radical inguinal lymphadenectomy improves oncological outcome [168]. One study reported poor long-term survival in patients with adjuvant inguinal and pelvic radiotherapy [169]. Other studies have likewise not demonstrated a patient benefit [168-174].

In one comparative retrospective study, adjuvant chemotherapy was far superior to adjuvant radiotherapy after radical inguinal lymphadenectomy in node-positive patients [157]. A large retrospective analysis of the SEER database (National Cancer Institute Surveillance, Epidemiology and End Results Program) of 2,458 penile cancer patients treated with either surgery alone or surgery plus EBRT concluded that the addition of adjuvant EBRT 'had neither a harmful nor a beneficial effect on CSS' [175].

Due to this lack of positive evidence, radiotherapy cannot be recommended outside of controlled trials for the treatment of lymph node disease in penile cancer. Prophylactic radiotherapy for cN0 disease is not indicated. Radiotherapy for advanced lymph node disease remains a palliative option.

*6.2.6 **Guidelines for treatment strategies for nodal metastases***

Regional lymph nodes	**Management of regional lymph nodes is fundamental in the treatment of penile cancer**	**Strength rating**
No palpable inguinal nodes (cN0)	Tis, Ta G1, T1G1: surveillance.	Strong
	> T1G2: invasive lymph node staging by either bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy.	Strong
Palpable inguinal nodes (cN1/cN2)	Radical inguinal lymphadenectomy.	Strong
Fixed inguinal lymph nodes (cN3)	Neoadjuvant chemotherapy followed by radical inguinal lymphadenectomy in responders.	Weak

Pelvic lymph nodes	Ipsilateral pelvic lymphadenectomy if two or more inguinal nodes are involved on one side (pN2) or if extracapsular nodal metastasis (pN3) reported.	Strong
Adjuvant chemotherapy	In pN2/pN3 patients after radical lymphadenectomy.	Strong
Radiotherapy	Not recommended for nodal disease except as a palliative option.	Strong

6.3 Chemotherapy

*6.3.1 **Adjuvant chemotherapy in node-positive patients after radical inguinal lymphadenectomy***

Multimodal treatment can improve patient outcome. Adjuvant chemotherapy after radical lymphadenectomy in node-positive patients has been reported in a few small and heterogeneous series [158-160]. Comparing different small-scale clinical studies is fraught with difficulty.

The value of adjuvant chemotherapy after radical inguinal lymphadenectomy in node-positive penile cancer was first demonstrated by a study which reported long-term (DFS) of 84% in 25 consecutive patients treated with twelve adjuvant weekly courses of vincristine, bleomycin, and methotrexate (VBM) during 1979-1990 and compared this to a historical control group of 38 consecutive node-positive patients with radical lymphadenectomy (with- or without adjuvant inguinal radiotherapy) who had achieved a DFS rate of only 39% [161].

The same group also published results of an adjuvant chemotherapy regimen with three courses of cisplatin and 5-FU with lower toxicity and even better results compared to VBM [176] (LE: 2b). The same group has published results of adjuvant chemotherapy with cisplatin, 5-FU plus paclitaxel or docetaxel (TPF), with three to four cycles after resection of pN2-3 disease [177]. Of 19 patients, 52.6% were disease-free after a median follow up of 42 months and tolerability was good. Results of adjuvant treatment with paclitaxel and cisplatin also improved outcome [178].

Therefore, the use of adjuvant chemotherapy is recommended, in particular when the administration of the triple combination chemotherapy is feasible and there is curative intent (LE: 2b). There are no data concerning adjuvant chemotherapy in stage pN1 patients. Adjuvant chemotherapy in pN1 disease is, therefore, recommended only in clinical trials.

*6.3.2 **Neoadjuvant chemotherapy in patients with fixed or relapsed inguinal nodes***

Bulky inguinal lymph node enlargement (cN3) indicates extensive lymphatic metastatic disease. Primary lymph node surgery is not generally recommended since complete surgical resection is unlikely and only a few patients will benefit from surgery alone.

Limited data is available on neoadjuvant chemotherapy before inguinal lymph node surgery. However, it allows for early treatment of systemic disease and down-sizing of the inguinal lymph node metastases. In responders, complete surgical treatment is possible with a good clinical response.

Results of neoadjuvant chemotherapy for bulky inguinal lymph node metastases were modest in retrospective studies including five to twenty patients treated with bleomycin-vincristine-methotrexate (BVM) or bleomycin-methotrexate-cisplatin (BMP) regimens [162, 163, 179], as well as in the confirmatory BMP trial of the Southwest Oncology Group [180]. However, treatment-related toxicity was unacceptable due to bleomycin-related mortality.

Cisplatin/5-FU (PF) chemotherapy achieved a response rate of 25-50% with more acceptable toxicity [181, 182]. Over a period of 30 years, five different neoadjuvant chemotherapy regimens were used in twenty patients [87], with long-term survival in 37% of responders who underwent radical lymph node surgery after neoadjuvant chemotherapy. In the EORTC cancer study 30992, 26 patients with locally advanced or metastatic disease received irinotecan and cisplatin chemotherapy. Although the study did not meet its primary endpoint (response rate), there were three cases of pathologically complete remissions [183].

A phase II trial evaluated treatment with four cycles of neoadjuvant paclitaxel, cisplatin, and ifosfamide (TIP). An objective response was reported in 15/30 patients, including three pathologically complete remissions (pCRs). The estimated median time to progression (TTP) was 8.1 months and the median OS was 17.1 months [164] (LE: 2a).

Hypothetical similarities between penile SCC and head and neck SCC led to the evaluation, in penile cancer, of chemotherapy regimens with an efficacy in head and neck SCC, including taxanes. The combination of cisplatin and 5-FU plus a taxane has been used in neoadjuvant and adjuvant settings [177]. An overall objective response rate of 44% was reported in 28 patients treated neoadjuvantly, including 14% pCR (LE: 2b). Similarly, a phase II trial with TPF using docetaxel instead of paclitaxel reported an objective response of 38.5% in 29 locally advanced or metastatic patients, although the study did not meet its primary endpoint. However, there was significant toxicity [184] (LE: 2a). Further evidence of the benefit of neoadjuvant chemotherapy was published recently [165].

Overall, these results support the recommendation that neoadjuvant chemotherapy using a cisplatin- and taxane-based triple combination should be used in patients with fixed, unresectable, nodal disease (LE: 2a).

There are hardly any data concerning the potential benefit of radiochemotherapy together with lymph node surgery in penile cancer. It should therefore only be used in controlled clinical trials [185].

*6.3.3 **Palliative chemotherapy in advanced and relapsed disease***

A recent retrospective study of 140 patients with advanced penile SCC reported that visceral metastases and an > 1 ECOG-performance status were independent prognostic factors, and that cisplatin-based regimens had better outcomes than non-cisplatin-based regimens after adjusting for prognostic factors [186] (LE: 3).

Before taxanes were introduced, chemotherapy data in penile cancer were limited by small numbers, patient heterogeneity and retrospective design (except for the EORTC trial [183]). Initial response rates ranged from 25% to 100%, with very few sustained responses and very few long-term survivors. The introduction of taxanes into penile cancer chemotherapy has enhanced the activity and efficacy of the regimens used [87, 162-164, 178-184, 187].

There are virtually no data on second-line chemotherapy in penile cancer. One report using second-line paclitaxel monotherapy reported a response rate of < 30% and no patient survived [188] (LE: 2a). Anecdotally, a benefit of second-line cisplatin with gemcitabine has been observed [189] (LE: 4).

*6.3.4 **Intra-arterial chemotherapy***

Intra-arterial chemotherapy which refers to intra-aortic application has been trialled in locally advanced cases, especially of cisplatin and gemcitabine in small case series [190-193]. Apart from a limited clinical response, the outcome was not significantly improved.

*6.3.5 **Targeted therapy***

Targeted drugs have been used as second-line treatment and they could be considered as single-agent treatment in refractory cases. Anti-epidermal growth factor receptor (EGFR) targeted monotherapy has been trialled [194], as EGFR is expressed in penile SCC [190, 191] and there are assumed similarities with head and neck SCC [190, 191]. There have been other studies, particularly with the anti-EGFR monoclonal antibodies panitumumab and cetuximab, without long-term response, however [195]. Some activity of tyrosine kinase inhibitors has been reported as well [193]. Further clinical studies are needed (LE: 4).

*6.3.6 **Guidelines for chemotherapy***

Recommendations	Strength rating
Offer patients with pN2-3 tumours adjuvant chemotherapy after radical lymphadenectomy (three to four cycles of cisplatin, a taxane and 5-fluorouracil or ifosfamide).	Strong
Offer patients with non-resectable or recurrent lymph node metastases neoadjuvant chemotherapy (four cycles of a cisplatin- and taxane-based regimen) followed by radical surgery.	Weak
Offer palliative chemotherapy to patients with systemic disease.	Weak

7. FOLLOW-UP

7.1 Rationale for follow-up

Early detection of recurrence increases the likelihood of curative treatment since local recurrence does not significantly reduce long-term survival if successfully treated [87, 196]. In contrast, disease that has spread to the inguinal lymph nodes greatly reduces the rate of long-term DSS. Follow-up is also important in the detection and management of treatment-related complications.

Local or regional nodal recurrences usually occur within two years of primary treatment [87]. After five years, all recurrences were either local or new primary lesions [87]. This supports an intensive follow-up regimen during the first two years, with a less intensive follow up later for a total of at least five years. Follow-up after five years may be omitted in motivated patients who will undertake regular self-examination reliably [87].

7.1.1 When and how to follow-up

After local treatment with negative inguinal nodes, follow-up should include physical examination of the penis and groins for local and/or regional recurrence. Additional imaging has no proven benefit. Follow-up also depends on the primary treatment modality. Histology from the glans should be obtained to confirm disease-free status following laser ablation or topical chemotherapy.

After potentially curative treatment for inguinal nodal metastases, CT or MRI imaging for the detection of systemic disease should be performed at three-monthly intervals for the first two years.

Although rare, late local recurrence may occur, with life-threatening metastases becoming very unusual after five years. Therefore, regular follow up can be stopped after five years, provided the patient understands the need to report any local changes immediately [197]. In patients unlikely to self-examine, long-term follow up may be necessary.

7.1.2 Recurrence of the primary tumour

Local recurrence is more likely with all types of local organ-sparing treatment but does not influence the rate of cancer-specific survival in contrast to regional lymph node recurrence [87, 196]. Local recurrence occurred during the first two years in up to 27% of patients treated with penis-preserving modalities [98]. After partial penectomy, the risk of local recurrence is about 4-5% [87, 98, 196].

Local recurrence is easily detected by physical examination, by the patient himself or his physician. Patient education is an essential part of follow-up and the patient should be urged to visit a specialist if any changes are seen.

7.1.3 Regional recurrence

Most regional recurrences occur during the first two years after treatment, irrespective of whether surveillance or invasive nodal staging were used. Although unlikely, regional recurrence can occur later than two years after treatment. It is therefore advisable to continue follow up in these patients [197]. The highest rate of regional recurrence (9%) occurs in patients managed by surveillance, while the lowest is in patients who have undergone invasive nodal staging by modified inguinal lymphadenectomy or DSNB and whose lymph nodes were negative (2.3%).

The use of US and fine needle aspiration cytology (FNAC) in suspicious cases has improved the early detection rate of regional recurrence [76, 198, 199]. There are no data to support the routine use of CT or MRI for the follow-up of inguinal nodes.

Patients who have had surgery for lymph node metastases without adjuvant treatment have an increased risk of regional recurrence of 19% [87]. Regional recurrence requires timely treatment by radical inguinal lymphadenectomy and adjuvant chemotherapy (see Section 6).

7.1.4 Guidelines for follow-up in penile cancer

	Interval of follow-up		**Examinations and investigations**	**Minimum duration of follow-up**	**Strength rating**
	Years one to two	Years three to five			
Recommendations for follow-up of the primary tumour					
Penile-preserving treatment	Three months	Six months	Regular physician or self-examination. Repeat biopsy after topical or laser treatment for penile intraepithelial neoplasia.	Five years	Strong
Amputation	Three months	One year	Regular physician or self-examination.	Five years	Strong
Recommendations for follow-up of the inguinal lymph nodes					
Surveillance	Three months	Six months	Regular physician or self-examination.	Five years	Strong
pN0 at initial treatment	Three months	One year	Regular physician or self-examination. Ultrasound with fine-needle aspiration biopsy optional.	Five years	Strong

pN+ at initial treatment	Three months	Six months	Regular physician or self-examination. Ultrasound with fine-needle aspiration cytology optional, computed tomography/ magnetic resonance imaging optional.	Five years	Strong

7.2 Quality of life

*7.2.1 **Consequences after penile cancer treatment***

In patients with long-term survival after penile cancer treatment, sexual dysfunction, voiding problems and cosmetic penile appearance may adversely affect the patient's QoL [200]. However, there is very little data on sexual function and QoL after treatment for penile cancer. In particular, there is heterogeneity of the psychometric tools used to assess QoL outcomes and further research is needed to develop disease-specific patient reported outcome measures for penile cancer.

Comparative studies

There are only two comparative studies in the literature reporting on the health-related quality of life (HRQoL) outcomes following surgery for localised penile cancer. One study compared wide local excision with glansectomy [201]. Among 41 patients there was reduction in post-operative International Index of Erectile Function (IIEF) and the authors concluded that local excision led to better sexual outcomes than glansectomy. In another study of 147 patients, the IIEF-15, the SF36 Health Survey and the Impact of Cancer questionnaire were used [202].

Compared to an age-matched population sample, men after partial penectomy reported significantly more problems with orgasm, cosmesis, life interference and urinary function than those who had undergone penile-sparing surgery (83% vs. 43%, $p < 0.0001$). Interestingly, there were no differences in erectile function, sexual desire, intercourse satisfaction or overall sexual satisfaction.

*7.2.2 **Sexual activity and quality of life after laser treatment***

A retrospective interview-based Swedish study after laser treatment for penile PeIN [104] in 58 out of 67 surviving patients with a mean age of 63 years, of whom 46 participated, reported a marked decrease in some sexual practices, such as manual stimulation, caressing and fellatio, but a general satisfaction rate with life overall and sexuality which was similar to that of the general Swedish population.

A large study on CO_2 laser treatment of penile cancer in 224 patients reported no problems with erectile or sexual function following treatment [91]. In another study [107], no sexual dysfunction occurred in nineteen patients treated.

*7.2.3 **Sexual activity after glans resurfacing***

In one study with ten patients [111], 7/10 completed questionnaires (IIEF-5 and a non-validated 9-item questionnaire) at six months. The median IIEF-5 score was 24 (no erectile dysfunction). All patients who were sexually active before treatment were active after three to five months, 7/7 stated that the sensation at the tip of their penis was either no different or better after surgery, and 5/7 patients felt that their sex life had improved. Overall patient satisfaction with glans resurfacing was high.

*7.2.4 **Sexual activity after glansectomy***

Two studies reported sexual function after glansectomy [112, 113]. In one (n = 68) with unclear methodology [113], 79% did not report any decline in spontaneous erection, rigidity or penetrative capacity after surgery, and 75% reported recovery of orgasm. In the other study [114], all twelve patients had returned to 'normal' sexual activity one month after surgery.

*7.2.5 **Sexual function after partial penectomy***

Sexual function after partial penectomy was reported by three studies [203-205]. In one with 18 patients with a mean age of 52 years, the IIEF scores were significantly worse for all domains of sexual function after surgery [203] and 55.6% of patients had erectile function that allowed sexual intercourse. In patients who did not resume sexual activity, 50% were ashamed of their small penis and missing glans, while another third blamed surgical complications. Of those who had resumed sexual intercourse, 66.7% reported the same frequency and level of sexual activity as before surgery, while 72.2% continued to have ejaculation and orgasm every time with sexual activity. Overall, only 33.3% maintained their pre-operative frequency of sexual intercourse and were satisfied with their sex life.

In another study, an 'Overall Sexual Functioning Questionnaire' was used in 14 patients with a median time of 11.5 months after surgery (range 6-72) [204]. Prior to surgery, all patients had had normal erectile function and intercourse at least once a month. In 9/14 patients, sexual function was 'normal' or 'slightly decreased', while 3/14 had had no sexual intercourse since surgery. Alei *et al.* reported an improvement in erectile function over time [205]. In a report of 25 patients after partial penectomy and neoglans formation, the IIEF-5, Quality of Erection Questionnaire (QEQ), Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) and Self-Esteem and Relationship (SEAR) were used. This study reported a high percentage of patient and partner satisfaction with surgical treatment and recovery of sexual function, self-esteem, and overall relationship satisfaction [206].

*7.2.6 **Quality of life and sexual function after total penectomy***

In ten patients with penile cancer evaluated after total amputation of the penis, there were significant effects on sexual life and overall QoL, although there were no negative implications in terms of partner relationships, self-assessment or the evaluation of masculinity [207].

*7.2.7 **Quality of life after partial penectomy***

Several qualitative and quantitative instruments have been used to assess 'psychological behaviour and adjustment' and 'social activity' as QoL indicators [204, 208]. Patient-reported fears were those of mutilation, loss of sexual pleasure and of cancer death and what this would mean for their families. The study reported no significant levels of anxiety and depression on the General Health Questionnaire-12 and the Hospital Anxiety and Depression Scale. 'Social activity' remained the same after surgery in terms of living conditions, family life and social interactions.

7.3 Total phallic reconstruction

There is very limited data about total phallic reconstruction following full or near-total penile amputation [137, 209, 210]. Although it is not possible to restore function without a penile prosthesis, cosmetically acceptable results can be obtained.

7.4 Specialised care

Since penile cancer is rare, patients should be referred to a centre with experience and expertise in local treatment, pathological diagnosis, chemotherapy and psychological support for penile cancer patients. Some countries have centralised the care of penile cancer patients (Sweden, Denmark, the Netherlands, the UK).

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9. CONFLICT OF INTEREST

All members of the Penile Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://uroweb.org/guideline/penile-cancer/.

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10. CITATION INFORMATION

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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Primary Urethral Carcinoma

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1. INTRODUCTION

1.1 Aims and scope

The aim of these guidelines is to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma. When the first carcinoma in the urinary tract is detected in the urethra, this is defined as primary urethral carcinoma, in contrast to secondary urethral carcinoma, which presents as recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary urethral carcinoma is reported after radical cystectomy for bladder cancer [1, 2] (see Chapter 7.3 of the European Association of Urology [EAU] Guidelines on Muscle-invasive and Metastatic Bladder Cancer [MIBC]) [2].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines Panel on MIBC is responsible for this publication. This is an international multidisciplinary group of clinicians, including urologists, oncologists, a pathologist, a radiotherapist and a radiologist. Members of this panel have been selected based on their expertise to represent the professionals treating patients suspected of suffering from urethral carcinoma. In the course of 2021 two patient representatives have formally joined the MIBC Guidelines Panel. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: https://uroweb.org/guideline/primary-urethral-carcinoma/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print and as an app for iOS and Android devices, presenting the main findings of the Primary Urethral Carcinoma Guidelines. These are abridged versions which may require consultation together with the full text version. The most recent scientific summary was published in 2020 [3].

1.4 Publication history & summary of changes

The Primary Urethral Carcinoma Guidelines were first published in 2013. This is the ninth update of this document.

1.4.1 Summary of changes

The literature for the complete document has been assessed and updated, where relevant. In particular for:

Section **6.3 Summary of evidence for prognosis**

Summary of evidence	LE
In locally advanced urothelial and squamous cell carcinoma of the urethra, treatment in academic centres improves overall survival.	3

Section 7.3.6 ***Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both males and females***

Recommendation	Strength rating
Refer patients with advanced urethral carcinoma to academic centres.	Strong

2. METHODS

2.1 Data identification

For the 2022 Primary Urethral Carcinoma Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. An updated systematic literature search was

performed to identify studies reporting data on urethral malignancies since the prior search, covering a time frame between October 20th and July 14th, 2021. Databases searched included Ovid (Medline), EMBASE and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. A total of 122 unique records were identified, retrieved, and screened for relevance. Seven new references were included in this 2022 publication. A detailed search strategy is available online: https://uroweb.org/guideline/primary-urethral-carcinoma/.

For each recommendation within the guidelines there is an accompanying online strength rating form, based on a modified GRADE methodology [4, 5]. These forms address a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [6];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [7]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

This document was peer-reviewed prior to publication in 2021.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Primary urethral carcinoma is considered a rare cancer, accounting for < 1% of all genitourinary malignancies [8] (ICD-O3 topography code: C68.0) [9]. In 2013, the prevalence of urethral carcinoma in the 28 European Union countries was 3,986 cases with an estimated annual incidence of 1,504 new cases, with a male/female prevalence of 2.9: 1 [10]. Likewise, in an updated analysis of the Surveillance, Epidemiology and End Results (SEER) database (2004-2016), the incidence of primary urethral carcinoma peaked in the > 75 years age group (7.6/million). The age-standardised rate was 4.3/million in men and 1.5/million in women and was almost negligible in those aged < 55 years (0.2/million) [11]. After matching for tumour and patient characteristics, women present with higher disease stage and exhibited higher cancer-specific mortality [12].

3.2 Aetiology

For male primary urethral carcinoma, various predisposing factors have been reported, including urethral strictures [13, 14], chronic irritation after intermittent catheterisation/urethroplasty [15-17], external beam irradiation therapy (EBRT) [18], radioactive seed implantation [19], chronic urethral inflammation/urethritis following sexually transmitted diseases (i.e., condylomata associated with human papilloma virus 16) [20, 21] and lichen sclerosis [14]. In female urethral carcinoma, urethral diverticula [22-24] and recurrent urinary tract infections [25] have been associated with primary urethral carcinoma. Mid-urethral sling meshes have not been associated with an increased risk of primary urethral carcinoma [26]. Clear-cell adenocarcinoma (AC) may also have a congenital origin [27, 28].

3.3 Histopathology

Both the Surveillance of Rare Cancers in Europe (RARECARE) project and SEER database have reported that urothelial carcinoma (UC) of the urethra is the predominant histological type of primary urethral cancer (54–65%), followed by squamous cell carcinoma (SCC) (16–22%) and AC (10–16%) [10, 29].

A SEER analysis of 2,065 men with primary urethral carcinoma (mean age 73 years) found that UC was most common (78%), and SCC (12%) and AC (5%) were significantly less frequent [30]. In women, AC is the more frequent histology (38–46.7%) followed by SCC (25.4–28%), UC (24.9–28%) and other histological entities (6%) [31, 32].

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Tumour, Node, Metastasis (UICC/TNM) staging system

In men and women, urethral carcinoma is classified according to the 8th edition of the TNM classification [9] (Table 4.1). It should be noted that there is a separate TNM staging system for prostatic UC [9]. Of note, for cancers occurring in the urethral diverticulum, stage T2 is not applicable as urethral diverticula are lacking periurethral muscle [33].

Table 4.1: TNM classification (8th edition) for urethral carcinoma [9]

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Urethra (male and female)	
Ta	Non-invasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder)
Urothelial (transitional cell) carcinoma of the prostate	
Tis pu	Carcinoma *in situ,* involvement of prostatic urethra
Tis pd	Carcinoma *in situ,* involvement of prostatic ducts
T1	Tumour invades subepithelial connective tissue (for tumours involving prostatic urethra only)
T2	Tumour invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T3	Tumour invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T4	Tumour invades other adjacent organs (invasion of the bladder or rectum)
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes
M - Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis

4.2 Tumour grade

Non-urothelial urethral carcinoma is graded by a trinomial system that differentiates between well-differentiated (G1), moderately-differentiated (G2), and poorly-differentiated tumours (G3). Table 4.2 lists the different grading systems according to the WHO 1973 and 2004 systems [34]. The 2004 classification corresponds to the 2016 WHO classification [35].

Table 4.2: Histopathological grading of urothelial and non-urothelial primary urethral carcinoma [34]

Urothelial urethral carcinoma	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Non-urothelial urethral carcinoma	
Gx	Tumour grade not assessable
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

4.3 Handling of tumour specimens

Specimen handling should follow the general rules as published by the International Collaboration on Cancer Reporting [36].

Table 4.3: Required and recommended elements for pathology reporting of carcinoma of the urethra in urethrectomy specimens [9, 36]

Required		**Recommended**	
Operative procedure		Clinical information	Previous history of urinary tract disease or distant metastasis
Additional specimens submitted			Previous therapy
Maximum tumour dimension	Cannot be assessed		Other clinical information
	No macroscopically visible tumour	Tumour focality	
	Maximum tumour dimension (largest tumour)	Other tumour dimensions (than maximum dimension) of the largest tumour	
Macroscopic tumour site		Block identification key	
Macroscopic extent of invasion		Associated epithelial lesions	
Histological tumour type	Histological subtype/ variant (urothelial carcinoma)	Extranodal spread for involved regional lymph node(s)	
Non-invasive carcinoma		Coexistent pathology	
Histological tumour grade		Ancillary studies	
Microscopic extent of invasion			
Lymphovascular invasion			
Margin status			
Regional lymph node status	No regional lymph nodes submitted		

4.4 Guideline for staging and classification systems

Recommendation	**Strength rating**
Use the 2017 TNM classification and 2004/2016 WHO grading systems for pathological staging and grading of primary urethral carcinoma.	Strong

5. DIAGNOSTIC EVALUATION AND STAGING

5.1 History

When becoming clinically apparent, most patients (45–57%) with primary urethral carcinoma present with symptoms associated with locally advanced disease (T3/T4) [37]. At initial presentation visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include; an extra-urethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%) or dyspareunia [37].

5.2 Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and digital rectal examination [38]. In women, further pelvic examination and palpation of the urethra should be performed. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to assess whether colorectal or gynaecological malignancies are present. Bilateral inguinal palpation should be done to assess the presence of enlarged LNs, describing location, size, and mobility [39].

5.3 Urinary cytology

Urinary cytology is part of the standard work-up of a patient with suspected primary urethral carcinoma. Reporting of urinary cytology findings should follow the Paris system [40]. However, the role of urinary cytology in primary urethral carcinoma is limited since its sensitivity ranges between 55% and 59% [41]. Detection rates depend on the underlying histological entity. In male patients, the sensitivity for UC and SCC was reported to be 80% and 50%, respectively, whereas in female patients, sensitivity was found to be 77% for SCC and 50% for UC [41].

5.4 Diagnostic urethrocystoscopy and biopsy

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location, and underlying histology [38]. Cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [42].

A cold-cup biopsy enables accurate tissue retrieval for histological analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histological diagnosis [43]. In patients with suspected UC of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (between the five and seven o'clock position from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [44].

To enable accurate pathological assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist. To obtain all relevant information, the collection, handling, and evaluation of biopsy specimen should follow the recommendations provided by the International Collaboration on Cancer Reporting (see Table 4.3) [36].

5.5 Imaging for diagnosis and staging

Radiological imaging of urethral carcinoma aims to assess local staging and to detect lymphatic and distant metastatic spread. In a recent multicentre study, the accuracy of cross-sectional imaging for clinical tumour and nodal staging predicting final pathological staging was found to be 72.9% and 70.6%, respectively [45]. Imaging work-up should include computed tomography of the chest, abdomen and pelvis for staging, including some form of CT urography with designated phases for optimal urothelial evaluation. Magnetic resonance imaging can be used to evaluate tumour location and size, as well as local tumour extent and presence of regional LN metastases, focusing in particular on inguinal and pelvic LNs [46-50].

For local staging, there is evidence that MRI is an accurate tool for monitoring tumour response to neoadjuvant chemoradiotherapy and evaluating the extent of local disease prior to exenterative surgery [51].

^{18}F-Fluorodeoxglucose positron emission tomography/magnetic resonance imaging has shown to improve the diagnostic evaluation in patients with metastatic disease [52].

5.6 Regional lymph nodes

In urethral carcinoma enlarged LNs often represent metastatic disease (~84% of patients) [54-56], which is in contrast to penile cancer where this is the case in ~41% of patients [53]. In men, lymphatics from the anterior urethra drain into the superficial- and deep inguinal LNs and, subsequently, to the pelvic (external, obturator

and internal iliac) LNs. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic LNs. In women, the lymph of the proximal third drains into the pelvic LN chains, whereas the distal two-thirds initially drain into the superficial- and deep inguinal nodes [57, 58].

5.7 Summary of evidence and guidelines for diagnostic evaluation and staging

Summary of evidence	LE
Patients with clinically enlarged inguinal or pelvic LNs often exhibit pathological LN metastasis.	3

Recommendations	Strength rating
Use urethrocystoscopy with biopsy and urinary cytology to diagnose urethral carcinoma.	Strong
Assess the presence of distant metastases by computed tomography of the thorax and abdomen/pelvis.	Strong
Use pelvic magnetic resonance imaging to assess the local extent of urethral tumour and regional lymph node enlargement.	Strong

6. PROGNOSIS

6.1 Long-term survival after primary urethral carcinoma

According to the RARECARE project, the one- and 5-year relative overall survival (OS) rates in patients with urethral carcinoma in Europe are 71% and 54%, respectively [10]. Based on longer follow-up, an analysis of the SEER database, comparing prognostic factors in rare pathological types of primary urethral carcinoma (n = 257) and common pathological groups (n = 2,651), reported 10-year OS rates of 42.4% and 31.9%, respectively [59]. Cancer-specific survival (CSS) rates at five and ten years were 68% and 60%, respectively [60]. Age (> 60 years), race (others vs. whites), T-stage (T3/T4 vs. Ta-T2) and M-stage (M1 vs. M0) were independent prognostic risk factors for OS and CSS in rare pathological variants [59].

6.2 Predictors of survival in primary urethral carcinoma

In Europe, 5-year OS rate does not substantially differ between the sexes [10, 32]. Prognostic factors of worse survival in patients with primary urethral carcinoma are:

- advanced age (> 65 years) and black race [10, 32, 61, 62];
- higher stage, grade, nodal involvement [55, 62] and metastasis [30];
- increased tumour size and proximal tumour location [30];
- underlying (non-urothelial) histology [10, 30, 61-64];
- presence of concomitant bladder cancer [42];
- extent of surgical treatment and treatment modality [30, 61, 62];
- treatment in academic centres [65];
- location of recurrence (urethral vs. non-urethral) [66].

Some limitations have to be considered when interpreting these results as the number of patients included in most studies were low [63].

6.3 Summary of evidence for prognosis

Summary of evidence	LE
Prognostic factors for survival in primary urethral carcinoma are: age, race, tumour stage and grade, nodal stage, presence of distant metastasis, histological type, tumour size, tumour location, concomitant bladder cancer and type and modality of treatment.	3
In locally advanced urothelial and squamous cell carcinoma of the urethra, treatment in academic centres improves overall survival.	3

7. DISEASE MANAGEMENT

7.1 Treatment of primary urethral carcinoma in males

Previously, treatment of male distal urethral carcinoma followed the procedure for penile cancer, with surgical excision of the primary lesion with a wide safety margin [38]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [67]. Therefore, in the treatment of distal urethral carcinoma the focus of clinicians has shifted towards improving functional outcomes and quality of life (QoL), while preserving oncological safety. A retrospective series found no evidence of local recurrence, even with < 5 mm resection margins (median follow-up: 17–37 months), in men with pT1-3N0-2 distal urethral carcinoma treated with well-defined penile-preserving surgery and additional iliac/inguinal lymphadenectomy (LND) for clinically suspected LN disease [68]. Similar results for the feasibility of penile-preserving surgery have also been reported in recent series [69, 70]. However, a series on patients treated with penile-preserving surgery for distal urethral carcinoma reported a higher risk of progression in patients with positive proximal margins, which was also more frequently observed in cases with lymphovascular and peri-neural invasion of the primary tumour [71].

7.1.1 Summary of evidence and guidelines for the treatment of primary urethral carcinoma in males

Summary of evidence	LE
In distal urethral tumours performing a partial urethrectomy with a minimal safety margin does not increase the risk of local recurrence.	3

Recommendations	Strength rating
Offer distal urethrectomy as an alternative to penile amputation in localised distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Ensure complete circumferential assessment of the proximal urethral margin if penile-preserving surgery is intended.	Strong

7.2 Treatment of localised primary urethral carcinoma in females

7.2.1 Urethrectomy and urethra-sparing surgery

In women with localised urethral carcinoma, to provide the highest chance of local cure, primary radical urethrectomy should include removal of all the peri-urethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and appendicovesicostomy for primary distal urethral lesions has been shown to provide satisfactory functional results in women [38].

Previous series have reported outcomes in women with mainly distal urethral tumours undergoing primary treatment with urethra-sparing surgery with or without additional radiotherapy (RT) compared to primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [72, 73]. In longer-term series with a median follow-up of 153–175 months, local recurrence rates in women undergoing partial urethrectomy with intra-operative frozen section analysis were 22–60%, and distal sleeve resection of > 2 cm resulted in secondary urinary incontinence in 42% of patients who subsequently required additional reconstructive surgery [72, 73].

Ablative surgical techniques, i.e., transurethral resection (TUR) or laser, used for small distal urethral tumours, have also resulted in considerable local failure rates of 16%, with a CSS rate of 50%. This emphasises the critical role of local tumour control in women with distal urethral carcinoma to prevent local and systemic progression [72].

7.2.2 Radiotherapy

In women, RT was investigated in several older series with a medium follow up of 91–105 months [74]. With a median cumulative dose of 65 Gy (range 40–106 Gy), the 5-year local control rate was 64% and 7-year CSS was 49% [74]. Most local failures (95%) occurred within the first two years after primary treatment [74]. The extent of urethral tumour involvement was found to be the only parameter independently associated with local tumour control but the type of RT (EBRT vs. interstitial brachytherapy) was not [74]. In one study, the addition of brachytherapy to EBRT reduced the risk of local recurrence by a factor of 4.2 [75]. Of note, pelvic toxicity in those achieving local control was considerable (49%), including urethral stenosis, fistula, necrosis, cystitis and/or haemorrhage, with 30% of the reported complications graded as severe [74].

7.2.3 Summary of evidence and guidelines for the treatment of localised primary urethral carcinoma in females

Summary of evidence	LE
In females with distal urethral tumours, urethra-sparing surgery and local RT represent alternatives to primary urethrectomy but are associated with increased risk of tumour recurrence and local toxicity.	3

Recommendations	Strength rating
Offer urethra-sparing surgery, as an alternative to primary urethrectomy, to females with distal urethral tumours, if negative surgical margins can be achieved intra-operatively.	Weak
Offer local radiotherapy, as an alternative to urethral surgery, to females with localised urethral tumours, but discuss local toxicity.	Weak

7.3 Multimodal treatment in locally advanced urethral carcinoma in both males and females

7.3.1 Introduction

Multimodal therapy in primary urethral carcinoma consists of definitive surgery plus chemotherapy with additional RT [76]. Multimodal therapy was often underutilised as shown by Cahn and colleagues (only 16%) in locally advanced disease notwithstanding promising results [76-79]. In a recent study monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex, and year of treatment ($p = 0.017$). Its use has decreased over time [80]. Treatment in academic centres was reported to result in higher utilisation of neoadjuvant- and multimodal treatment and improved OS in patients with locally advanced urothelial- and squamous cell primary urethral carcinoma [65].

7.3.2 Preoperative cisplatin-based chemotherapy

Retrospective studies reported that modern cisplatin-based combination chemotherapy regimens can be effective in advanced primary urethral carcinoma providing prolonged survival even in LN-positive disease. Moreover, they emphasised the critical role of surgery after chemotherapy to achieve long-term survival in patients with locally advanced urethral carcinoma.

In a series of 124 patients, 39 (31%) were treated with peri-operative platinum-based chemotherapy for advanced primary urethral carcinoma (twelve patients received neoadjuvant chemotherapy, six received neoadjuvant chemoradiotherapy and 21 adjuvant chemotherapy). Patients who received neoadjuvant chemotherapy or chemoradiotherapy for locally advanced primary urethral carcinoma (≥ cT3 and/or cN+) appeared to demonstrate improved survival compared to those who underwent upfront surgery with or without adjuvant chemotherapy [81]. Another retrospective series including 44 patients with advanced primary urethral carcinoma, reported outcomes on 21 patients who had preoperatively received cisplatin-based combination chemotherapy according to the underlying histologic subtype. The overall response rate for the various regimens was 72% and the median OS 32 months [54].

7.3.3 Chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of local RT with concurrent chemotherapy as an alternative to surgery in locally advanced SCC has been reported in several series. This approach offers a potential for genital preservation [82-86]. The largest, and recently updated, retrospective series reported outcomes in 25 patients with primary locally advanced SCC of the urethra treated with two cycles of 5-fluorouracil and mitomycin C with concurrent EBRT. A complete clinical response was observed in ~80% of patients. The 5-year OS and disease-specific survival was 52% and 68%, respectively. In this updated series, salvage surgery, initiated only in non-responders or in case of local failure, was not reported to be associated with improved survival [82].

A large retrospective cohort study in patients with locally advanced urethral carcinoma treated with adjuvant RT and surgery vs. surgery alone demonstrated that the addition of RT improved OS [87].

7.3.4 Salvage treatment in recurrent primary urethral carcinoma after surgery for primary treatment

A multicentre study reported that patients who were treated with surgery as primary therapy and underwent surgery or RT-based salvage treatment for recurrent solitary or concomitant urethral disease, demonstrated similar survival rates compared to patients who never developed recurrence after primary treatment [66].

7.3.5 Treatment of regional lymph nodes

Nodal control in urethral carcinoma can be achieved either by regional LN dissection [38], RT [74] or chemotherapy [54]. Currently, there is still no clear evidence supporting prophylactic bilateral inguinal and/or pelvic LND in all patients with urethral carcinoma [56]. However, in patients with clinically enlarged inguinal/pelvic LNs or invasive tumours, regional LND should be considered as initial treatment since cure might still be achievable with limited disease [38]. It was recently shown that in patients with invasive urethral SCC and cN1-2 disease, inguinal LND conferred an OS benefit [56].

7.3.6 Summary of evidence and guidelines for multimodal treatment in advanced urethral carcinoma in both males and females

Summary of evidence	LE
In locally advanced urethral carcinoma, cisplatin-based chemotherapy with curative intent prior to surgery might improve survival compared to chemotherapy alone, or surgery followed by chemotherapy.	3
In locally advanced SCC of the urethra, treatment with chemoradiotherapy might be an alternative to surgery.	3
In locally advanced urothelial and squamous cell carcinoma of the urethra, treatment in academic centres improves overall survival.	3

Recommendations	Strength rating
Refer patients with advanced urethral carcinoma to academic centres.	Strong
Discuss treatment of patients with locally advanced urethral carcinoma within a multidisciplinary team of urologists, radiation-oncologists, and oncologists.	Strong
In locally advanced urethral carcinoma, use cisplatin-based chemotherapeutic regimens with curative intent prior to surgery.	Weak
In locally advanced squamous cell carcinoma (SCC) of the urethra, offer the combination of curative radiotherapy (RT) with radiosensitising chemotherapy for definitive treatment and genital preservation.	Weak
Offer salvage surgery or RT to patients with urethral recurrence after primary treatment.	Weak
Offer inguinal lymph node (LN) dissection to patients with limited LN-positive urethral SCC.	Weak

7.4 Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent BCG instillation is effective in patients with Ta or Tis prostatic urethral carcinoma [88]. Likewise, patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not [89]. Risk of understaging local extension of prostatic urethral cancer at TUR is high in patients with ductal or stromal involvement [90]. In smaller series, response rates to BCG in patients with prostatic duct involvement have been reported to vary between 57% and 75% [88, 91]. Some earlier series have reported superior oncological results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement [92, 93]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a LN mapping study found that twelve patients had positive LNs, with an increased proportion located above the iliac bifurcation [94].

7.4.1 Summary of evidence and guidelines for the treatment of urothelial carcinoma of the prostate

Summary of evidence	LE
Patients undergoing TUR of the prostate for prostatic urothelial carcinoma prior to BCG treatment show superior complete response rates compared to those who do not.	3

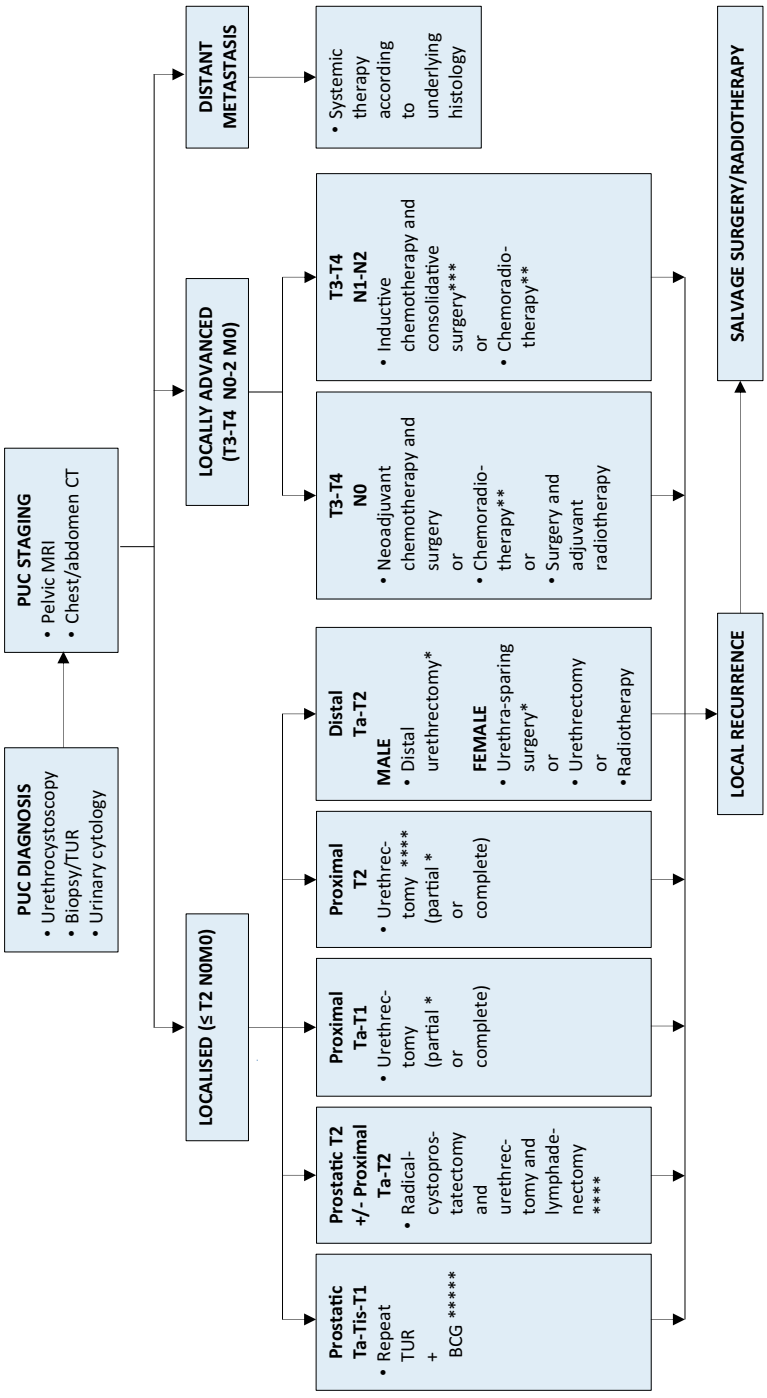
Recommendations	Strength rating
Offer a urethra-sparing approach with transurethral resection (TUR) and bacillus-Calmette Guérin (BCG) to patients with non-invasive urethral carcinoma or carcinoma *in situ* of the prostatic urethra and prostatic ducts.	Strong
In patients not responding to BCG, or in patients with extensive ductal or stromal involvement, perform a cystoprostatectomy with extended pelvic lymphadenectomy.	Weak

7.5 Metastatic disease

There is no data addressing management of metastatic disease in primary urethral carcinoma patients. Systemic therapy in metastatic disease should be selected based on the histology of the tumour. The EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer can be followed if UC is the predominant histology [2]. Even though urethral carcinoma patients have been included in large clinical trials on immunotherapy, so far, in terms of response rates, no subgroup analyses are available [95].

In addition, there is an urgent clinical need to better address the role of local palliative treatment strategies in primary urethral carcinoma including surgery, which has shown to impact positively on QoL aspects in selected patients with advanced genital cancers [96].

Figure 7.1: Management of primary urethral carcinoma



* Ensure complete circumferential assessment if penile-preserving/urethra-sparing surgery or partial urethrectomy is intended.

** Squamous cell carcinoma.

*** Regional lymphadenectomy should be considered in clinically enlarged lymph nodes.
**** Consider neoadjuvant chemotherapy.
***** In extensive or BCG-unresponsive disease: consider (primary) cystoprostatectomy +/- urethrectomy + lymphadenectomy.

BCG = bacillus Calmette-Guérin; CT = computed tomography; MRI = magnetic resonance imaging; PUC = primary urethral carcinoma; TUR = transurethral resection.

8. FOLLOW-UP

Given the low incidence of primary urethral carcinoma, follow-up has not been systematically investigated. Therefore, it seems reasonable to tailor surveillance regimens to patients' individual risk factors (see Section 6.2). In patients undergoing urethra-sparing surgery, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocystoscopy and cross-sectional imaging despite the lack of specific data.

8.1 Research priorities

There are clear gaps in the clinical literature related to the diagnosis, management and follow-up of patients with primary urethral carcinoma. As this is a rare disease, data will likely become available through quality registries and datasets, similar to those currently being set up by the eUrogen initiative.

The Panel identified the following topics as of interest:

- The (long-term) efficacy of urethral-sparing surgery and chemoradiotherapy for genital preservation in localised and locally advanced tumours;
- The prognostic impact of neoadjuvant and adjuvant treatment modalities in locally advanced disease;
- The therapeutic benefit and clinical safety of programmed cell death (ligand)-1 inhibitors for the treatment of advanced primary urethral carcinoma.

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10. CONFLICT OF INTEREST

All members of the Muscle-invasive and Metastatic Bladder Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is open access available on the European Association of Urology website: http://www.uroweb.org/guidelines/primary-urethral-carcinoma/.

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Renal Cell Cancer (RCC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of RCC.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise and judgement when making treatment decisions for individual patients, but rather help to focus decisions whilst also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The RCC Guidelines Panel is an international group of clinicians consisting of urological surgeons, oncologists, methodologists, a pathologist and a radiologist, with particular expertise in the field of renal cancer care. Since 2015, the Panel has incorporated a patient advocate to provide a consumer perspective for its guidelines. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/renalcellcarcinoma/.

1.3 Acknowledgement

The RCC Guidelines Panel is most grateful for the continued methodological and scientific support provided by Prof.Dr. O. Hes (pathologist, Pilzen, Czech Republic) for two sections of this document: Histological diagnosis and Other renal tumours.

1.4 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices, presenting the main findings of the RCC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU RCC Guidelines [1]. All documents can be accessed on the EAU website: http://uroweb.org/guideline/renal-cell-carcinoma/.

1.5 Publication history and summary of changes

1.5.1 Publication history

The EAU RCC Guidelines were first published in 2000. This 2022 RCC Guidelines document presents a substantial update of the 2021 publication.

1.5.2 Summary of changes

All chapters of the 2022 RCC Guidelines have been updated, based on the 2021 version of the Guidelines. References have been added throughout the document.

New data have been included in the following sections, resulting in changed evidence summaries and recommendations in:

5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC

Recommendations	Strength rating
Offer brain CT/MRI in metastatic patients when systemic therapy or cytoreductive nephrectomy is considered.	Weak
Do not perform a renal tumour biopsy of cystic renal masses unless a significant solid component is visible at imaging.	Strong

5.5 Summary of evidence and recommendations for genetic assessment of RCC

Summary of evidence	LE
Hereditary kidney cancer is thought to account for 5–8% of all kidney cancer cases, though that number is likely an underestimate.	3
In case of renal cancer, if patient's age is 46 years or younger, and/or with bilateral or multifocal tumours and/or with a first or second-degree relative with RCC and/or with close blood relative with a known pathogenic variant and/or with specific histologic characteristics (see text), the risk or hereditary cancer is significantly higher.	3
Hereditary RCC detection has unique implications for decision-making and follow-up.	3

Recommendations	Strength rating
Perform a genetic evaluation in patients aged ≤ 46 years, with bilateral or multifocal tumours and/or a first or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant and/or specific histologic characteristics which suggest the presence of a hereditary form of RCC.	Strong
Refer patients to a cancer geneticist or to a comprehensive clinical care centre in case of suspected hereditary kidney cancer.	Strong

7.1.2.2.4 Summary of evidence and recommendations for the treatment of localised RCC

Recommendation	Strength rating
Do not offer an extended lymph node dissection to patients with organ-confined disease.	Weak

7.1.3.4 Summary of evidence and recommendations for radical and partial nephrectomy techniques

Summary of evidence	LE
Transperitoneal and retroperitoneal laparoscopic PN do not differ in in post-operative surgical and medical complications, positive surgical margins and kidney function.	2a

Recommendation	Strength rating
Intensify follow-up in patients with a positive surgical margin, especially in upstaged pT3a patients.	Weak

7.2.4.3 Summary of evidence and recommendations for the management of RCC with venous tumour thrombus

Recommendation	Strength rating
During nephrectomy, remove clinically enlarged lymph nodes for staging, prognosis and follow-up implications.	Weak

7.2.5.1 Summary of evidence and recommendations for neoadjuvant and adjuvant therapy

Summary of evidence	LE
Adjuvant TKI therapy does not improve OS after nephrectomy.	1b
Adjuvant pembrolizumab after nephrectomy in patients with high-risk RCC improves progression-free survival.	1b
In one RCT, in selected intermediate/high- or high-risk patients or M1 patients without evidence of disease, adjuvant pembrolizumab improved disease-free survival.	1b

Recommendation	Strength rating
Offer adjuvant pembrolizumab to patients with clear-cell (cc) RCC following surgery with curative intent with a risk of recurrence as defined in the trial.*	Weak

**pT2 G4 or pT3 any G; pT4 any G; pN+ Any G.*

7.3.2.6 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	LE
A single-arm prospective and retrospective study support that oligometastases can be observed for up to 16 months before systemic therapy is required due to progression.	2a

Recommendations	Strength rating
Perform a confirmatory axial scan of disease status prior to metastasectomy to rule out rapid progressive metastatic disease which requires systemic treatment.	Weak
Before initiating systemic therapy for oligometastases that cannot be resected, discuss with your patient a period of observation until progression is confirmed.	Weak

7.4.2.4 Summary of evidence and recommendations for targeted therapy in clear-cell metastatic RCC

Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

7.4.4.1.2 Summary of evidence and recommendations for immunotherapy in clear-cell metastatic RCC

Summary of evidence	LE
Sequencing systemic therapy	
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade 3-5 toxicity ranging between 61-72% and 1% of treatment-related deaths.	1b

Recommendation	Strength rating
Treatment-naïve patients	
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naïve vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong

7.4.4.1.3.1 Summary of evidence and recommendation for targeted therapy in RCC with sarcomatoid features

Summary of evidence	LE
Immune checkpoint inhibitor combination therapy was superior to sunitinib in terms of PFS and OS in trial subset analysis of cc-RCC with sarcomatoid features.	2a

Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

7.4.4.2.1 Summary of evidence and recommendation for targeted therapy in non-clear-cell metastatic RCC

Summary of evidence	LE
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
In non-cc-mRCC, sunitinib improved PFS over everolimus in a systematic review of phase II trials and subgroups of patients.	2a

Recommendation	Strength rating
Offer sunitinib to patients with other non-ccRCC subtypes than papillary RCC.	Weak

7.4.4.3.1 Summary of evidence and recommendations for targeted therapy in papillary metastatic RCC

Summary of evidence	LE
Cabozantinib improved PFS over sunitinib in patients with advanced pRCC without additional molecular testing.	2a
Savolitinib improved PFS over sunitinib in patients with MET-driven advanced pRCC.	2a
Pembrolizumab resulted in long-term median OS in a single arm study in the pRCC subgroup.	2a

Recommendations	Strength rating
Offer cabozantinib to patients with advanced papillary RCC (pRCC) without molecular testing.	Weak
Offer savolitinib to patients with MET-driven advanced pRCC.	Weak
Offer pembrolizumab to patients with advanced pRCC without molecular testing.	Weak

7.5.1 ***Summary of evidence and recommendation on locally recurrent RCC after treatment of localised disease***

Summary of evidence	LE
Surgical or percutaneous treatment of local recurrences in absence of systemic progression should be considered, especially in absence of adverse prognostic parameters and favourable performance status.	3
The most optimal modality of local treatment for locally recurrent RCC after nephron-sparing procedures or nephrectomy is not defined.	3

Recommendation	Strength rating
Offer local treatment of locally recurrent disease when technically possible and after balancing adverse prognostic features, comorbidities and life expectancy.	Weak

2. METHODS

2.1 Data identification

For the 2022 Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature for the chapters as listed in Table 2.1.

A broad and comprehensive scoping search was performed, which was limited to studies representing high certainty of evidence (i.e., systematic reviews with or without meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies only for therapeutic interventions, and systematic reviews and prospective studies with well-defined reference standards for diagnostic accuracy studies) published in the English language. In case no higher level data exists for a particular topic, lower level evidence is considered for inclusion. The search was restricted to articles published between June 25th, 2020 and May 28th, 2021. Databases covered included Medline, EMBASE, and the Cochrane Library. After de-duplication, a total of 2,644 unique records were identified, retrieved and screened for relevance.

A total of 71 new references have been included in the 2022 RCC Guidelines publication. A search strategy is published online: https://uroweb.org/guideline/renal-cell-carcinoma/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2]. Each strength rating form addresses a number of key elements, namely:

1. the overall quality of the evidence which exists for the recommendation; references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);

4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation.

The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. The strength rating forms will be available online.

Specific chapters were updated by way of systematic reviews, commissioned and undertaken by the Panel, based on prioritised topics or questions. These reviews were performed using standard Cochrane systematic review methodology: http://www.cochranelibrary.com/about/aboutcochranesystematic-reviews.html.

Table 2.1: Description of update and summary of review methodology

Chapter	Brief description of review methodology
1. Introduction	Not applicable.
2. Methods	Not applicable.
3. Epidemiology, aetiology and pathology	This chapter was updated by a narrative review, based on a structured literature assessment.
4. Staging and grading classification systems	This chapter was updated by a narrative review, based on a structured literature assessment. Section 3.4.5.1 (Treatment of angiomyolipoma) was updated by means of a systematic review [5].
5. Diagnostic evaluation	Section 5.2 (Diagnostic imaging) was revised based on a systematic review [6]. The remainder of the chapter was updated by a structured literature assessment.
6. Prognosis	This chapter was updated by a narrative review, based on a structured literature assessment.
7. Treatment (Disease management)	Sections 7.1.2 and 7.2.4 (Treatment of localised and locally advanced disease) were revised based on an updated systematic review. Sub-section 7.1.4.4.2 (Cryoablation versus partial nephrectomy) was updated by means of a SR [7]. Some aspects of Section 7.4.2 (Targeted therapy for metastatic RCC) were updated by way of a Cochrane systematic review [8]. Section 7.4.4.2 (Non-clear-cell metastatic RCC) was updated by means of a SR [9]. The remainder of this section has been extensively restructured now, also including separate sections on non-clear-cell RCC and von Hippel-Lindau (VHL)-related RCC.
8. Follow-up in RCC & Surveillance following radical or partial nephrectomy or ablative therapies	This chapter was updated by a narrative review, based on a structured literature assessment. The findings of a prospective database set up by the RCC Panel have been included [10, 12].

Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://uroweb.org/guidelines/. A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

All publications ensuing from systematic reviews have been peer reviewed. The 2021 print of the RCC Guidelines was peer-reviewed prior to publication.

2.3 Future goals

The RCC Guideline Panel supports the focus on patient-reported outcomes as well as the development of clinical quality indicators. A number of key quality indicators for this patient group have been selected:

- the proportion of patients undergoing thorax computed tomography (CT) for staging of pulmonary metastasis;
- proportion of patients with T1aN0M0 tumours undergoing nephron-sparing surgery (NSS) as first treatment;
- the proportion of patients with metastatic RCC (mRCC) offered systemic therapy;
- the proportion of patients who undergo minimally invasive or operative treatment as first treatment who die within 30 days.

The Panel have set up a database to investigate current practice in follow-up of RCC patients in a number of European centres. Assessing patterns of recurrence and use of imaging techniques are primary outcomes for this project.

The results of ongoing and new systematic reviews will be included in future updates of the RCC Guidelines:

- What is the best treatment option for ≥ T2 tumours?
- Adjuvant targeted therapy for renal cell carcinoma at high risk for recurrence;
- Systematic review of prevalence of intraperitoneal recurrences following robotic/laparoscopic partial nephrectomy;
- Systematic review of individual, unit and hospital surgical volume for radical and partial nephrectomy and their impact on outcomes;
- RECUR database analysis of recurrent disease/follow-up.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries [13, 14]. In Europe, and worldwide, the highest incidence rates are found in the Czech Republic and Lithuania [14]. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe leading to approximately 99,200 new RCC cases and 39,100 kidney cancer-related deaths within the European Union in 2018 [13, 14]. In Europe, overall mortality rates for RCC increased until the early 1990s, with rates generally stabilising or declining thereafter [15]. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend [13, 14].

Renal cell carcinoma is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics [16]. There is a 1.5:1 predominance in men over women with a higher incidence in the older population [14, 17].

3.2 Aetiology

Established risk factors include lifestyle factors such as (hazard ratio [HR]: 1.23-1.58), obesity (HR 1.71), BMI (> 35 vs. < 25), and hypertension (HR: 1.70) [14, 17]. 50.2% of patients with RCC are current or former smokers. By histology, the proportions of current or former smokers range from 38% in patients with chromophobe carcinoma to 61.9% in those with collecting duct/medullary carcinoma [18]. In a recent systematic review diabetes was also found to be detrimental [19]. Having a first-degree relative with kidney cancer is also associated with an increased risk of RCC. Moderate alcohol consumption appears to have a protective effect for reasons as yet unknown, while any physical activity level also seems to have a small protective effect [14, 19-23]. A number of other factors have been suggested to be associated with higher or lower risk of RCC, including specific dietary habits and occupational exposure to specific carcinogens, but the literature is inconclusive [17]. The most effective prophylaxis is to avoid cigarette smoking and reduce obesity [14, 17].

3.2.1 *Summary of evidence and recommendation for epidemiology, aetiology and pathology*

Summary of evidence	LE
Several verified risk factors have been identified including smoking, obesity and hypertension. These are considered definite risk factors for RCC.	2a

Recommendation	Strength rating
Increase physical activity, eliminate cigarette smoking and in obese patients reduce weight are the primary preventative measures to decrease risk of RCC.	Strong

3.3 Histological diagnosis

Renal cell carcinomas comprise a broad spectrum of histopathological entities described in the 2016 World Health Organization (WHO) classification [16]. There are three main RCC types: clear cell (ccRCC), papillary (pRCC type I and II) and chromophobe (chRCC). The RCC type classification has been confirmed by cytogenetic and genetic analyses [16, 24] (LE: 2b). Collecting duct carcinoma and other rare renal tumours are discussed in Section 3.3.

Histological diagnosis includes, besides RCC type; evaluation of nuclear grade, sarcomatoid features, vascular invasion, tumour necrosis, and invasion of the collecting system and peri-renal fat, pT, or even pN categories. The four-tiered WHO/ISUP (International Society of Urological Pathology) grading system has replaced the Fuhrman grading system [16].

3.3.1 *Clear-cell RCC*

Overall, clear-cell RCC (ccRCC) is well circumscribed and a capsule is usually absent. The cut surface is golden-yellow, often with haemorrhage and necrosis. Loss of chromosome 3p and mutation of the von Hippel-Lindau (VHL) gene at chromosome 3p25 are frequently found. The loss of von Hippel-Lindau protein function contributes to tumour initiation, progression, and metastases. The 3p locus harbours at least four additional ccRCC tumour suppressor genes (*UTX, JARID1C, SETD2, PBRM1*) [24]. In general, ccRCC has a worse prognosis compared to pRCC and chRCC, but this difference disappears after adjustment for stage and grade [25, 26]. For details about prognosis, see Section 6.3 – Histological factors.

3.3.2 *Papillary RCC*

Papillary RCC is the second most commonly encountered morphotype of RCC. Papillary RCC has traditionally been subdivided into two types [16]. Type I and II pRCC, which were shown to be clinically and biologically distinct; pRCC type I is associated with activating germline mutations of *MET* and pRCC type II is associated with activation of the NRF2-ARE pathway and at least three subtypes [27]. Type II pRCC presents a heterogenous group of tumours and future substratification is expected, e.g., oncocytic pRCC [16].

A typical histology of pRCC type I (narrow papillae without any binding, and only microcapillaries in papillae) explains its typical clinical signs. Narrow papillae without any binding and a tough pseudocapsule explain the ideal rounded shape (Pascal's law) and fragility (specimens have a "minced meat" structure). Tumour growth causes necrotisation of papillae, which is a source of hyperosmotic proteins that cause subsequent "growth" of the tumour, fluid inside the tumour, and only a serpiginous, contrast-enhancing margin. Stagnation in the microcapillaries explain the minimal post-contrast attenuation on CT. Papillary RCC type 1 can imitate a pathologically changed cyst (Bosniak IIF or III). The typical signs of pRCC type 1 are as follows: an ochre colour, more frequently exophytic, extrarenal growth, low grade, and low malignant potential; over 75% of these tumours can be treated by NSS surgery. A substantial risk of renal tumour biopsy tract seeding exists (12.5%), probably due to the fragility of the tumour papillae [28]. Papillary RCC type I is more common and generally considered to have a better prognosis than pRCC type II [16, 26, 29].

3.3.3 *Chromophobe RCC*

Overall, chRCC is a pale tan, relatively homogenous and tough, well-demarcated mass without a capsule. Chromophobe RCC cannot be graded by the Fuhrman grading system because of its innate nuclear atypia. An alternative grading system has been proposed, but has yet to be validated [16]. Loss of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 are typical genetic changes [16]. The prognosis is relatively good, with high five-year recurrence-free survival (RFS), and ten-year cancer-specific survival (CSS) [30]. The five- and ten-year recurrence-free survival rates were 94.3% and 89.2%, respectively. Recurrent disease developed in 5.7% of patients, and 76.5% presented with distant metastases with 54% of metastatic disease diagnoses involving a single organ, most commonly bone. Recurrence and death after surgically resected chRCC is rare. For completely excised lesions ≤ pT2a without coagulative necrosis or sarcomatoid features, prognosis is excellent [31]. The new WHO/ISUP grading system merges former entity 'hybrid oncocytic chromophobe tumour' with chRCC.

3.4 Other renal tumours

Other renal tumours constitute the remaining renal cortical tumours. These include a variety of uncommon, sporadic, and familial carcinomas, some only recently described, as well as a group of unclassified carcinomas. A summary of these tumours is provided in Table 3.1, but some clinically relevant tumours and extremely rare entities are mentioned below.

*3.4.1 **Renal medullary carcinoma***

Renal medullary carcinoma (RMC) is a very rare tumour, comprising < 0.5% of all RCCs [32], predominantly diagnosed in young adults (median age 28 years) with sickle haemoglobinopathies (including sickle cell trait). It is mainly centrally located with ill-defined borders. Renal medullary carcinoma is one of the most aggressive RCCs [33, 34] and most patients (~67%) will present with metastatic disease [33, 35]. Even patients who present with seemingly localised disease may develop macrometastases shortly thereafter, often within a few weeks (for treatment see chapter 7).

*3.4.2 **Carcinoma associated with end-stage renal disease; acquired cystic disease-associated RCC***

Cystic degenerative changes (acquired cystic kidney disease [ACKD]) and a higher incidence of RCC, are typical features of end-stage renal disease (ESRD). Renal cell carcinomas of native end-stage kidneys are found in approximately 4% of patients. Their lifetime risk of developing RCCs is at least ten times higher than in the general population. Compared with sporadic RCCs, RCCs associated with ESRD are generally multicentric and bilateral, found in younger patients (mostly male), and are less aggressive. Whether the relatively indolent outcome of tumours in ESRD is due to the mode of diagnosis or a specific ACKD-related molecular pathway still has to be determined. Although the histological spectrum of ESRD tumours is similar to that of sporadic RCC; pRCC occur relatively more frequently [36, 37]. A specific subtype of RCC occurring only in end-stage kidneys has been described as Acquired Cystic Disease-associated RCC (ACD-RCC) with indolent clinical behaviour, likely due to early detection in patients with ESRD on periodic follow-up [16, 24, 38].

*3.4.3 **Papillary adenoma***

These tumours have a papillary or tubular architecture of low nuclear grade and may be up to 15 mm in diameter, or smaller [39], according to the WHO 2016 classification [16].

*3.4.4 **Hereditary kidney tumours***

Five to eight percent of RCCs are hereditary; to date there are ten hereditary RCC syndromes associated with specific germline mutations, RCC histology, and comorbidities. Hereditary RCC syndromes are often suggested by family history, age of onset and presence of other lesions typical for the respective syndromes. Median age for hereditary RCC is 37 years; 70% of hereditary RCC tumours are found in the lowest decile (46 years old) of all RCC tumours [40]. Hereditary kidney tumours are found in the following entities: VHL syndrome, hereditary pRCC, Birt-Hogg-Dube syndrome, hereditary leiomyomatosis and RCC (HLRCC), tuberous sclerosis, germline succinate dehydrogenase (SDH) mutation, non-polyposis colorectal cancer syndrome, hyperparathyroidism-jaw tumour syndrome, phosphatase and tensin homolog (PTEN) hamartoma syndrome (PHTS), constitutional chromosome 3 translocation, familial non-syndromic ccRCC and BAP1 associated RCC [41]. Renal medullary carcinoma can be included because of its association with hereditary haemoglobinopathies [39, 42-44].

Patients with hereditary kidney cancer syndromes may require repeated surgical intervention [45, 46]. In most hereditary RCCs nephron-sparing approaches are recommended. The exceptions are HLRCC and SDH syndromes for which immediate surgical intervention is recommended due to the aggressive nature of this lesion. For other hereditary syndromes such as VHL, surveillance is recommended until the largest tumour reaches 3 cm in diameter, to reduce interventions [47]. Active surveillance (AS) for VHL, SDH and HLRCC should, in individual patients, follow the growth kinetics, size and location of the tumours, rather than apply a standardised follow-up interval. Regular screening for both renal and extra-renal lesions should follow international guidelines for these syndromes. Multidisciplinary and co-ordinated care should be offered, where appropriate [48]. In HLRCC, renal screening in relatives detects early-stage RCCs [49], with HLRCC RCCs appearing to have unique molecular profiles.

Although not hereditary, somatic fusion translocations of *TFE3* and *TFEB* may affect 15% of patients with RCC younger than 45 years and 20-45% of children and young adults diagnosed with RCC [50].

A recent phase II trial demonstrated clinical activity of an oral HIF-2α (hypoxia-inducible factor) inhibitor MK-6482 in VHL patients [51]. Additional information on treatment of VHL can be found in Section 7.4.4.

3.4.5 ***Angiomyolipoma***

Angiomyolipoma (AML) is a benign mesenchymal tumour, which can occur sporadically or as part of tuberous sclerosis complex [52]. Overall prevalence is 0.44%, with 0.6% in female and 0.3% in male populations. Only 5% of these patients present with multiple AMLs [53]. Angiomyolipoma belongs to a family of so-called PEComas (perivascular epithelioid cell tumours), characterised by the proliferation of perivascular epithelioid cells. Some PEComas can behave aggressively and can even produce distant metastases. Classic AMLs are completely benign [16, 39, 54]. Ultrasound (US), CT, and magnetic resonance imaging (MRI) often lead to the diagnosis of AMLs due to the presence of adipose tissue; however, in fat-poor AML, diagnostic imaging cannot reliably identify these lesions. Percutaneous biopsy is rarely useful. Renal tumours that cannot be clearly identified as benign during the initial diagnostic work-up should be treated according to the recommendations provided for the treatment of RCC in these Guidelines. In tuberous sclerosis, AML can be found in enlarged lymph nodes (LNs), which does not represent metastatic spread but a multicentric spread of AMLs. In rare cases, an extension of a non-malignant thrombus into the renal vein or inferior vena cava can be found, associated with an angiotrophic-type growth of AML. Epithelioid AML, a very rare variant of AML, consists of at least 80% epithelioid cells [39, 54]. Epithelioid AMLs are potentially malignant with a highly variable proportion of cases with aggressive behaviour [55]. Criteria to predict the biological behaviour in epithelioid AML were proposed by the WHO 2016 [39, 54]. Angiomyolipoma, in general, has a slow and consistent growth rate, and minimal morbidity [5].

In some cases, larger AMLs can cause local pain. The main complication of AMLs is spontaneous bleeding in the retroperitoneum or into the collecting system, which can be life threatening. Bleeding is caused by spontaneous rupture of the tumour. Little is known about the risk factors for bleeding, but it is believed to increase with tumour size and may be related to the angiogenic component of the tumour that includes irregular blood vessels [5]. The major risk factors for bleeding are tumour size, grade of the angiogenic component, and the presence of tuberous sclerosis [56, 57].

3.4.5.1 *Treatment*

Active surveillance is the most appropriate option for most AMLs (48%). In a group of patients on AS, only 11% of AMLs showed growth, and spontaneous bleeding was reported in 2%, resulting in active treatment in 5% of patients [5, 58] (LE: 3). The association between AML size and the risk of bleeding remains unclear and the traditionally used 4-cm cut-off should not *per se* trigger active treatment [5]. When surgery is indicated, NSS is the preferred option, if technically feasible. Main disadvantages of less invasive selective arterial embolisation (SAE) are more recurrences and a need for secondary treatment (0.85% for surgery vs. 31% for SAE). For thermal ablation only limited data are available, and this option is used less frequently [5].

Active treatment (SAE, surgery or ablation) should be instigated in case of persistent pain, ruptured AML (acute or repeated bleeding) or in case of a very large AML. Specific patient circumstances may influence the choice to offer active treatment; such as patients at high risk of abdominal trauma, females of childbearing age or patients in whom follow-up or access to emergency care may be inadequate. Selective arterial embolisation is an option in case of life-threatening AML bleeding.

In patients diagnosed with tuberous sclerosis, size reduction of often bilateral AMLs can be induced by inhibiting the mTOR pathway using everolimus, as demonstrated in RCTs [59, 60]. In a small phase II trial (n = 20), efficacy of everolimus was demonstrated in sporadic AML as well. A 25% or greater reduction in tumour volume at four and six months was demonstrated in 55.6% and 71.4% of patients, respectively. Twenty percent of patients were withdrawn due to toxicities and 40% self-withdrew from the study due to side effects [61].

3.4.6 ***Renal oncocytoma***

Oncocytoma is a benign tumour representing 3–7% of all solid renal tumours and its incidence increases to 18% when tumours < 4 cm are considered [16, 58]. The diagnostic accuracy of imaging modalities (CT, MRI) in renal oncocytoma is limited and histopathology remains the only reliable diagnostic modality [16, 58]. However, the new imaging technology ^{99m}Tc-sestamibi (SestaMIBI, MIBI) SPECT/CT has shown promising initial results for the differentiation between benign and low grade RCC [62]. Standard treatment for renal oncocytoma is similar to that of other renal tumours; surgical excision by partial- or radical nephrectomy (RN) with subsequent histopathological verification. However, due to the inability of modern imaging techniques to differentiate benign from malignant renal masses, there is a renewed interest in renal mass biopsy (RMB) prior to surgical intervention. Accuracy of the biopsy and management of advanced/progressing oncocytomas need to be considered in this context since oncocytic renal neoplasms diagnosed by RMB at histological examination after surgery showed oncocytoma in only 64.6% of cases. The remainder of the tumours were mainly chRCC (18.7% including 6.3% hybrid oncocytic/chromophobe tumours which have now been grouped histologically with chRCC) [16], other RCCs (12.5%), and other benign lesions (4.2%) [63]. The majority of oncocytomas slowly progress in size with an annual growth rate < 14 mm [64-66]. Preliminary data show that AS may be a safe option to manage oncocytoma in appropriately selected patients. Potential triggers to change management of patients on AS are not well defined [67].

Table 3.1: Other renal cortical tumours, and recommendations for treatment (strength rating: weak) [16]

Entity	Clinical relevant notes	Malignant potential	Treatment
Sarcomatoid variants of RCC	Sign of high-grade transformation without being a distinct histological entity.	High	Surgery. Nivolumab and ipilimumab. Sunitinib, gemcitabine plus doxorubicin is also an option [68].
Multilocular cystic renal neoplasm of low malignant potential	Formerly multilocular cystic RCC.	Benign	Nephron-sparing surgery (NSS).
Carcinoma of the collecting ducts of Bellini	Rare, often presenting at an advanced stage (N+ 44% and M1, 33% at diagnosis). The hazard ratio (HR) for CSS in comparison with ccRCC is 4.49 [26].	High, very aggressive. Median survival is 30 months [69].	Surgery. Response to targeted therapies is poor [70].
Renal medullary carcinoma	Very rare. Mainly young black men with sickle cell trait.	High, very aggressive, median survival is five months [69].	Surgery. Different chemotherapy regimens, radiosensitive.
Translocation RCC (TRCC) Xp11.2	Rare, mainly younger patients < 40, more common in females. Less commonly, *TFEB* located on the short arm of chromosome 6 (6p21) [71].	High	Surgery. Vascular endothelial growth factor (VEGF)-targeted therapy.
Translocation RCC t(6;11)		Low/intermediate	Surgery, NSS. VEGF-targeted therapy.
Mucinous tubular and spindle cell carcinoma	Tumour is associated with the loop of Henle.	Intermediate	Surgery, NSS.
Acquired cystic disease-associated RCC		Low	Surgery, NSS.
Clear-cell papillary RCC		Low	Surgery, NSS.
Hereditary leiomyomatosis and RCC-associated RCC	Rare, germline mutation of the fumarate hydratase gene [16]. 21% lifetime risk of RCC [49].	High	Surgery. No data about treatment of metastatic disease. Imaging screening in relatives is recommended [49].
Tubulocystic RCC	Mainly men, imaging can be Bosniak III or IV.	Low (90% indolent)	Surgery, NSS.
Succinate dehydrogenase-deficient RCC	Rare.	Variable	Surgery, NSS.
Metanephric tumours	Divided into metanephric adenoma, adenofibroma, and metanephric stromal tumours.	Benign	Surgery, NSS.
Cystic nephroma/Mixed epithelial and stromal tumour	Term renal epithelial and stromal tumours (REST) is used as well. Imaging – Bosniak type III or II/IV.	Low/benign	Surgery, NSS.
Oncocytoma	3-7% of all renal tumours. Imaging characteristics alone are unreliable when differentiating between oncocytoma and RCC. Histopathological diagnosis remains the reference standard.	Benign	Observation (when histologically confirmed). NSS. See Section *3.4.6.*

Renal cysts	Simple cysts are frequently occurring, while occurring septa, calcifications and solid components require follow-up and/or management.	Malignant or benign	Treatment or follow-up recommendation based on Bosniak classification. See Table 5.1

*3.4.7 **Cystic renal tumours***

Cystic renal lesions are classified according to the Bosniak classification (see Section 5.2.5). Bosniak I and II cysts are benign lesions which do not require follow-up [72]. Bosniak IV cysts are mostly (83%) malignant tumours [73] with pseudocystic changes only. Bosniak IIF and III cysts remain challenging for clinicians. The differentiation of benign and malignant tumour in categories IIF/III is based on imaging, mostly CT, with an increasing role of MRI and contrast-enhanced ultrasound (CEUS). Computed tomography shows poor sensitivity (36%) and specificity (76%; κ [kappa coefficient] = 0.11) compared with 71% sensitivity and 91% specificity (κ = 0.64) for MRI and 100% sensitivity and 97% specificity for CEUS (κ = 0.95) [74]. Surgical and radiological cohorts pooled estimates show a prevalence of malignancy of 0.51 (0.44–0.58) in Bosniak III and 0.89 (0.83–0.92) in Bosniak IV cysts, respectively. In a systematic review, less than 1% of stable Bosniak IIF cysts showed malignancy during follow-up. Twelve percent of Bosniak IIF cysts had to be reclassified to Bosniak III/IV during radiological follow-up, with 85% of these showing malignancy, which is comparable to the malignancy rates of Bosniak IV cysts [72]. The updated Bosniak classification strengthens the classification and includes also MRI diagnostic criteria [75].

The most common histological type for Bosniak III cysts is ccRCC with pseudocystic changes and low malignant potential [76, 77]; multilocular cystic renal neoplasm of low malignant potential ([MCRNLMP], formerly mcRCC (see Section 3.2 and Table 3.1); pRCC type I (very low malignant potential); benign multilocular cyst; benign group of renal epithelial and stromal tumours (REST); and other rare entities. Surgery in Bosniak III cysts will result in over-treatment in 49% of the tumours which are lesions with a low malignant potential. In view of the excellent outcome of these patients in general, a surveillance approach is an alternative to surgical treatment [72, 75, 78, 79].

3.5 Summary of evidence and recommendations for the management of other renal tumours

Summary of evidence	LE
A variety of renal tumours exist of which approximately 15% are benign.	1b
Recent histological work up of Bosniak III cysts shows low risk of malignant potential.	2

3.6 Recommendations for the management of other renal tumours

Recommendations	Strength rating
Manage Bosniak type III cysts the same as localised RCC, or offer active surveillance (AS).	Weak
Manage Bosniak type IV cysts the same as localised RCC.	Strong
Treat angiomyolipoma (AML) with selective arterial embolisation or nephron-sparing surgery, in: • large tumours (a recommended threshold of intervention does not exist); • females of childbearing age; • patients in whom follow-up or access to emergency care may be inadequate; • persistent pain or acute or repeated bleeding episodes.	Weak
Offer systemic therapy to patients at need for therapy with surgically unresectable AMLs not amendable to embolisation or surgery.	Weak
Prior to management, perform pre-operative renal mass biopsies in patients with unclear kidney lesions.	Weak
Offer AS to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation.	Weak
Off radical nephrectomy to patients with localised renal medullary carcinoma.	Weak
Base systemic therapy for renal medullary carcinoma on chemotherapy regiments containing cisplatinum such as cisplatin plus gemcitabine.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Staging

The Tumour Node Metastasis (TNM) classification system is recommended for clinical and scientific use [80], but requires continuous re-assessment [16, 81]. A supplement was published in 2012, and the latter's prognostic value was confirmed in single and multi-institution studies [82, 83]. Tumour size, venous invasion, renal capsular invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system (Table 4.1). However, some uncertainties remain:

- The sub-classification of T1 tumours using a cut-off of 4 cm might not be optimal in NSS for localised cancer.
- The value of size stratification of T2 tumours has been questioned [84].
- Renal sinus fat invasion might carry a worse prognosis than perinephric fat invasion, but, is nevertheless included in the same pT3a stage group [85-88] (LE: 3).
- Sub T-stages (pT2b, pT3a, pT3c and pT4) may overlap [83].
- For adequate M staging, accurate pre-operative imaging (chest and abdominal CT) should be performed [89, 90] (LE: 4).

Table 4.1: 2017 TNM classification system [80]

T - Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour ≤ 7 cm or less in greatest dimension, limited to the kidney		
	T1a	Tumour ≤ 4 cm or less	
	T1b	Tumour > 4 cm but ≤ 7 cm	
T2	Tumour > 7 cm in greatest dimension, limited to the kidney		
	T2a	Tumour > 7 cm but ≤ 10 cm	
	T2b	Tumours > 10 cm, limited to the kidney	
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia		
	T3a	Tumour extends into the renal vein or its segmental branches, or invades the pelvicalyceal system or invades perirenal and/or renal sinus fat, but not beyond Gerota fascia*	
	T3b	Tumour grossly extends into the vena cava below diaphragm	
	T3c	Tumour grossly extends into vena cava above the diaphragm or invades the wall of the vena cava	
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)		
N - Regional Lymph Nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
M - Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
pTNM stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

A help desk for specific questions about TNM classification is available at http://www.uicc.org/tnm.
**Adapted based on the American Joint Committee on Cancer (AJCC), 8th Edn. 2017 [91].*

4.2 Anatomic classification systems

Objective anatomic classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, the R.E.N.A.L. nephrometry score, the C-index, an Arterial Based Complexity (ABC) Scoring System and Zonal NePhRO scoring system, have been proposed to standardise the

description of renal tumours [92-94]. These systems include assessment of tumour size, exophytic/endophytic properties, proximity to the collecting system and renal sinus, and anterior/posterior or lower/upper pole location.

The use of such a system is helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of partial nephrectomy (PN) and tumour ablation series. However, when selecting the most optimal treatment option, anatomic scores must be considered together with patient features and surgeon experience.

5. DIAGNOSTIC EVALUATION

5.1 Symptoms

Many renal masses remain asymptomatic until the late disease stages. The majority of RCCs are detected incidentally by non-invasive imaging investigating various non-specific symptoms and other abdominal diseases [95] (LE: 3). In a recent prospective observational cohort study, 60% of patients overall, 87% of patients with stage 1a renal tumours and 36% of patients with stage III or IV disease presented incidentally [96]. The classic triad of flank pain, visible haematuria, and palpable abdominal mass is rare (6–10%) and correlates with aggressive histology, advanced disease and poorer outcomes [96-98] (LE: 3). Paraneoplastic syndromes are found in approximately 30% of patients with symptomatic RCCs [99] (LE: 4). Some symptomatic patients present with symptoms caused by metastatic disease, such as bone pain or persistent cough [100] (LE: 3).

*5.1.1 **Physical examination***

Physical examination has a limited role in RCC diagnosis. However, the following findings should prompt radiological examinations:

- palpable abdominal mass;
- palpable cervical lymphadenopathy;
- non-reducing varicocele and bilateral lower extremity oedema, which suggests venous involvement.

*5.1.2 **Laboratory findings***

Commonly assessed laboratory parameters are serum creatinine, glomerular filtration rate (GFR), complete cell blood count, erythrocyte sedimentation rate, liver function study, alkaline phosphatase, lactate dehydrogenase (LDH), serum corrected calcium [101], coagulation study, and urinalysis (LE: 4). For central renal masses abutting or invading the collecting system, urinary cytology and possibly endoscopic assessment should be considered in order to exclude urothelial cancer (LE: 4).

Split renal function should be estimated using renal scintigraphy in the following situations [102, 103] (LE: 2b):

- when renal function is compromised, as indicated by increased serum creatinine or significantly decreased GFR;
- when renal function is clinically important; e.g., in patients with a solitary kidney or multiple or bilateral tumours.

Renal scintigraphy is an additional diagnostic option in patients at risk of future renal impairment due to comorbid disorders.

5.2 Imaging investigations

Most renal tumours are diagnosed by abdominal US or CT performed for other medical reasons [95] (LE: 3). Renal masses are classified as solid or cystic based on imaging findings.

*5.2.1 **Presence of enhancement***

With solid renal masses, the most important criterion for differentiating malignant lesions is the presence of enhancement [104] (LE: 3). Traditionally, US, CT and MRI are used for detecting and characterising renal masses. Most renal masses are diagnosed accurately by imaging alone.

*5.2.2 **Computed tomography or magnetic resonance imaging***

Computed tomography or MRI are used to characterise renal masses. Imaging must be performed unenhanced, in an early arterial phase, and in a parenchymal phase with intravenous contrast material to demonstrate enhancement. In CT imaging, enhancement in renal masses is determined by comparing Hounsfield units (Hus) before, and after, contrast administration. A change of fifteen HU, or more, in the solid

tumour parts demonstrates enhancement and thus vital tumour parts [105] (LE: 3). Computed tomography or MRI allows accurate diagnosis of RCC, but cannot reliably distinguish oncocytoma and fat-free AML from malignant renal neoplasms [106-109] (LE: 3). Abdominal CT provides information on [110]:

- function and morphology of the contralateral kidney [111] (LE: 3);
- primary tumour extension;
- venous involvement;
- enlargement of locoregional LNs;
- condition of the adrenal glands and other solid organs (LE: 3).

Abdominal contrast-enhanced CT angiography is useful in selected cases when detailed information on the renal vascular supply is needed [112, 113]. If the results of CT are indeterminate, CEUS is a valuable alternative to further characterise renal lesions [6, 114-116] (LE: 1b).

Magnetic resonance imaging may provide additional information on venous involvement if the extent of an inferior vena cava (IVC) tumour thrombus is poorly defined on CT [117-120] (LE: 3). In MRI, especially high-resolution T2-weighted images provide a superior delineation of the uppermost tumour thrombus, as the inflow of the enhanced blood may be reduced due to extensive occlusive tumour thrombus growth in the inferior vena cava. The T2-weighted image with its intrinsic contrast allows a good delineation [120].

Magnetic resonance imaging is indicated in patients who are allergic to intravenous CT contrast medium and in pregnancy without renal failure [120, 121] (LE: 3). Magnetic resonance imaging allows the evaluation of a dynamic enhancement without radiation exposure. Advanced MRI techniques such as diffusion-weighted (DWI) and perfusion-weighted imaging are being explored for renal mass assessment [122]. Recently, the use of multiparametric MRI (mpMRI) to diagnose ccRCC via a clear cell likelihood score (ccLS) in small renal masses was reported [123]. The ccLS is a 5-tier classification that denotes the likelihood of a mass representing ccRCC, ranging from 'very unlikely' to 'very likely'. The authors prospectively validated the diagnostic performance of ccLS in 57 patients with cT1a tumours and found a high diagnostic accuracy. The diagnostic performance of mpMRI-based ccLS was further validated in a larger retrospective cohort (n = 434) across all tumour sizes and stages [124], and ccLS was found to be an independent prognostic factor for identifying ccRCC. The system is promising and deserves further validation.

For the diagnosis of complex renal cysts (Bosniak IIF-III) MRI may be preferable. The accuracy of CT is limited in these cases, with poor sensitivity (36%) and specificity (76%; $\kappa = 0.11$); MRI, due to a higher sensitivity for enhancement, showed a 71% sensitivity and 91% specificity ($\kappa = 0.64$). Contrast-enhanced US showed high sensitivity (100%) and specificity (97%), with a negative predictive value of 100% ($\kappa = 0.95$) [74].

In younger patients who are worried about the radiation exposure of frequent CT scans, MRI may be offered as alternative although only limited data exist correlating diagnostic radiation exposure to the development of secondary cancers [125].

A recent systematic review and meta-analysis [126] compared the diagnostic performance of CEUS vs. contrast-enhanced CT and contrast-enhanced MRI (CEMRI) in the assessment of benign and malignant cystic and solid renal masses. Sixteen studies were included in the pooled analysis. The results suggested comparable diagnostic performance of CEUS compared with CECT (pooled sensitivity 0.96 (95% CI: 0.94-0.98), vs. 0.90 (95% CI: 0.86-0.93), for studies with a final diagnosis of benign or malignant renal masses by pathology), and CEUS vs. CEMRI (pooled sensitivity 0.98 (95% CI: 0.94-1.0), vs. 0.78 (95% CI: 0.66-0.91), for studies with final diagnosis by pathology report or reaffirmed diagnosis by follow-up imaging without pathology report. However, there were significant limitations in the data, including very few studies for CEMRI, clinical and statistical heterogeneity and inconsistency, and high risks of confounding.

*5.2.3 **Other investigations***

Renal arteriography and inferior venacavography have a limited role in the work-up of selected RCC patients (LE: 3). In patients with any sign of impaired renal function, an isotope renogram and total renal function evaluation should be considered to optimise treatment decision-making [102, 103] (LE: 2a). Positron-emission tomography (PET) is not recommended [6, 127] (LE: 1b).

*5.2.4 **Radiographic investigations to evaluate RCC metastases***

Chest CT is accurate for chest staging [89, 90, 128-130] (LE: 3). Use of nomograms to calculate risk of lung metastases have been proposed based on tumour size, clinical stage and presence of systemic symptoms [131, 132]. These are based on large, retrospective datasets, and suggest that chest CT may be omitted in patients with cT1a and cN0, and without systemic symptoms, anaemia or thrombocythemia, due to the low

incidence of lung metastases (< 1%) in this group of patients. There is a consensus that most bone metastases are symptomatic at diagnosis; thus, routine bone imaging is not generally indicated [128, 133, 134] (LE: 3). However, bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms [133, 135, 136] (LE: 3). A recent prospective comparative blinded study involving 92 consecutive mRCC patients treated with first-line VEGFR-tyrosine kinase inhibitor (TKI) (median follow-up 35 months) found that whole-body DWI/MRI detected a statistically significant higher number of bony metastases compared with conventional thoraco-abdomino-pelvic contrast-enhanced CT, with higher number of metastases being an independent prognostic factor for progression-free survival (PFS) and overall survival (OS) [137].

The incidence of brain metastasis without neurological symptoms was retrospectively evaluated in 1,689 mRCC patients, selected to be included in 68 clinical trials between 2001-2019 [138]. All patients had a mandatory brain screening by CT/MRI. There were 72 patients (4.3%) diagnosed with occult brain metastases, 39% multi-focal. Most patients (61%) were in IMDC intermediate risk, and 26% had a favourable risk. A majority (86%) of the patients had ≥ 2 extracranial metastatic sites, including lung metastases in 92%. After predominantly radiotherapy, performed in 93%, a median patient's overall survival of 10.3 months (range 7.0–17.9 months) was observed.

*5.2.5 **Bosniak classification of renal cystic masses***

This system classifies renal cysts into five categories, based on CT imaging appearance, to predict malignancy risk [139, 140] (LE: 3), and also advocates treatment for each category (Table 5.1). A new updated Bosniak classification has been proposed that strengthens the classification and includes MRI diagnostic criteria [75]; however, it requires further validation. The management of cystic renal tumours is also discussed in Section 3.4.7.

Table 5.1: Bosniak classification of renal cysts [130]

Bosniak category	Features	Work-up
I	Simple benign cyst with a hairline-thin wall without septa, calcification, or solid components. Same density as water and does not enhance with contrast medium.	Benign
II	Benign cyst that may contain a few hairline-thin septa. Fine calcification may be present in the wall or septa. Uniformly high-attenuation lesions < 3 cm in size, with sharp margins without enhancement.	Benign
IIF	These may contain more hairline-thin septa. Minimal enhancement of a hairline-thin septum or wall. Minimal thickening of the septa or wall. The cyst may contain calcification, which may be nodular and thick, with no contrast enhancement. No enhancing soft-tissue elements. This category also includes totally intra-renal, non-enhancing, high attenuation renal lesions ≥ 3 cm. Generally well-marginated.	Follow-up, up to five years. Some are malignant.
III	These are indeterminate cystic masses with thickened irregular walls or septa with enhancement.	Surgery or active surveillance – see Chapter 7. Over 50% are malignant.
IV	Clearly malignant containing enhancing soft-tissue components.	Surgery. Most are malignant.

5.3 Renal tumour biopsy

*5.3.1 **Indications and rationale***

Percutaneous renal tumour biopsy can reveal histology of radiologically indeterminate renal masses and can be considered in patients who are candidates for AS of small masses, to obtain histology before ablative treatments, and to select the most suitable medical and surgical treatment strategy in the setting of metastatic disease [141-146] (LE: 3).

A multicentre study assessing 542 surgically removed small renal masses showed that the likelihood of benign findings at pathology is significantly lower in centres where biopsies are performed (5% vs. 16%), suggesting that biopsies can reduce surgery for benign tumours and the potential for short-term and long-term morbidity associated with these procedures [147].

Renal biopsy is not indicated for comorbid and frail patients who can be considered only for conservative management (watchful waiting) regardless of biopsy results. Due to the high diagnostic accuracy of abdominal imaging, renal tumour biopsy is not necessary in patients with a contrast-enhancing renal mass for whom surgery is planned (LE: 4).

Core biopsies of cystic renal masses have a lower diagnostic yield and accuracy and are not recommended, unless areas with a solid pattern are present (Bosniak IV cysts) [141, 144, 148] (LE: 2b/3). Histological characterisation by percutaneous biopsy of undefined retroperitoneal masses at imaging may be useful for decision making especially in the younger population.

*5.3.2 **Technique***

Percutaneous sampling can be performed under local anaesthesia with needle core biopsy and/or fine needle aspiration (FNA). Biopsies can be performed under US or CT guidance, with a similar diagnostic yield [144, 149] (LE: 2b). Eighteen-gauge needles are ideal for core biopsies, as they result in low morbidity and provide sufficient tissue for diagnosis [141, 145, 150] (LE: 2b). A coaxial technique allowing multiple biopsies through a coaxial cannula should always be used to avoid potential tumour seeding [141, 145] (LE: 3).

Core biopsies are preferred for the characterisation of solid renal masses while a combination with FNA can provide complimentary results and improve accuracy for complex cystic lesions [148, 151, 152] (LE: 2a). A systematic review and meta-analysis of the diagnostic performance and complications of renal tumour biopsy was performed by the Panel, including 57 publications and a total of 5,228 patients. Needle core biopsies were found to have better accuracy for the diagnosis of malignancy compared with FNA [148]. Other studies showed that solid pattern, larger tumour size and exophytic location are predictors of a diagnostic core biopsy [141, 144, 149] (LE: 2b).

*5.3.3 **Diagnostic yield and accuracy***

In experienced centres, core biopsies have a high diagnostic yield, specificity, and sensitivity for the diagnosis of malignancy. The above-mentioned meta-analysis showed that sensitivity and specificity of diagnostic core biopsies for the diagnosis of malignancy are 99.1% and 99.7%, respectively [148] (LE: 2b). However, 0–22.6% of core biopsies are non-diagnostic (8% in the meta-analysis) [142-146, 149, 150, 153] (LE: 2a). If a biopsy is non-diagnostic, and radiologic findings are suspicious for malignancy, a further biopsy or surgical exploration should be considered (LE: 4). Repeat biopsies have been reported to be diagnostic in a high proportion of cases (83-100%) [141, 154-156].

Accuracy of renal tumour biopsies for the diagnosis of tumour histotype is good. The median concordance rate between tumour histotype on renal tumour biopsy and on the surgical specimen of the following PN or RN was 90.3% in the pooled analysis [148].

Assessment of tumour grade on core biopsies is challenging. In the pooled analysis the overall accuracy for nuclear grading was poor (62.5%), but significantly improved (87%) using a simplified two-tier system (high vs. low grade) [148] (LE: 2a).

The ideal number and location of core biopsies are not defined. However, at least two good quality cores should be obtained and necrotic areas should be avoided to maximise diagnostic yield [141, 144, 157, 158] (LE: 2b). Peripheral biopsies are preferable for larger tumours, to avoid areas of central necrosis [159] (LE: 2b). In cT2 or greater renal masses, multiple core biopsies taken from at least four separate solid enhancing areas in the tumour were shown to achieve a higher diagnostic yield and a higher accuracy to identify sarcomatoid features, without increasing the complication rate [160].

*5.3.4 **Morbidity***

Overall, percutaneous biopsies have a low morbidity [148]. Tumour seeding along the needle tract has been regarded as anecdotal in large series and pooled analyses on renal tumour biopsies. Especially the coaxial technique has been regarded as a safe method to avoid any seeding of tumour cells. However, authors recently reported on seven patients in whom tumour seeding was identified on histological examination of the resection specimen after surgical resection of RCC following diagnostic percutaneous biopsy [161]. Six of the seven cases were of the pRCC type. The clinical significance of these findings is still uncertain but only one of these patients developed local tumour recurrence at the site of the previous biopsy [161].

Spontaneously resolving subcapsular/perinephric haematomas are reported in 4.3% of cases in a pooled analysis, but clinically significant bleeding is unusual (0–1.4%; 0.7% in the pooled analysis) and generally self-limiting [148].

Percutaneous biopsy of renal hilar masses is technically feasible with a diagnostic yield similar to that of cortical masses, but with significantly higher post-procedural bleeding compared with cortical masses [162].

5.3.5 *Genetic assessment*

Renal cancer can be related to an inherited or *de novo* monogenic germline alteration and this recognition has significant implications [163]. Hereditary kidney cancer is thought to account for 5–8% of all kidney cancer cases, although this number is likely an underestimation since a more recent study found germline mutations in up to 38% of all metastatic kidney cancer patients [164] (see Section 3.4.4. Hereditary kidney tumours). Patients with a germline predisposition to kidney cancer often require multidisciplinary approaches, it is critical for clinicians to be familiar with how and when referral for counselling is warranted, methods of genetic testing, implications of the findings, screening of at-risk (non-renal) organs, and the screening protocol for family members. Well-defined renal cancer management strategies exist, and specific therapeutic strategies are available or in development (see Section 3.4.4). Lack of a syndromic manifestation does not exclude a genetic contribution to cancer development. Moreover, other genetic components or polymorphisms are heritable and may confer a mildly increased risk. When several risk alleles are present, they can significantly increase cancer risk.

Many factors are associated with an increased risk of hereditary renal cancer syndromes. For instance, even in the absence of clinical manifestations and personal/family history, an age of onset of 46 years or younger should trigger consideration for genetic counselling/germline mutation testing [40]. Moreover, presence of bilateral or multifocal tumours/cysts and/or a first- or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant significantly increases the risk to detect hereditary cancer. The presence of renal cysts can be associated with BHD and VHL, and form part of the clinical diagnostic spectrum. Moreover, specific histologic characteristics can support differential diagnosis of a particular renal cell carcinoma syndrome (e.g., multifocal papillary histology, hereditary leiomyomatosis-associated RCC, RCC with fumarate hydratase deficiency, multiple chromophobe, oncocytoma or oncocytic hybrid, succinate dehydrogenase-deficient RCC histology). Finally, additional tuberous sclerosis complex criteria should be assessed in individuals with AML [40, 165-173].

If additional risk factors are established in a patient, referral to a comprehensive clinical care centre, or a hospital with demonstrated expertise in managing hereditary cancer syndromes, will provide a dedicated working team, tailored clinical decisions, research translational program, appropriate patient psychosocial support, and prospective collection of clinical data and biological samples. This can contribute to a better patient's care and further improvements in cancer care.

5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC

Summary of evidence	LE
Contrast-enhanced multi-phasic CT has a high sensitivity and specificity for characterisation and detection of RCC, invasion, tumour thrombus and mRCC.	2a
Magnetic resonance imaging has a slightly higher sensitivity and specificity for small cystic renal masses and tumour thrombi as compared to CT.	2a
Contrast-enhanced ultrasound has a high sensitivity and specificity for characterisation of renal masses.	2a
Renal mass biopsies are associated with reduced overtreatment of benign masses and offers patients additional information (i.e., grade, subtype) for an informed decision regarding optimal management.	3
Ultrasound, power-Doppler US and positron-emission tomography CT have a low sensitivity and specificity for detection and characterisation of RCC.	2a

Recommendations	Strength rating
Use multi-phasic contrast-enhanced computed tomography (CT) of abdomen and chest for the diagnosis and staging of renal tumours.	Strong
Omit chest CT in patients with incidentally noted cT1a disease due to the low risk of lung metastases in this cohort.	Weak
Use magnetic resonance imaging (MRI) to better evaluate venous involvement, reduce radiation or avoid intravenous CT contrast medium.	Weak
Use non-ionising modalities, including MRI and contrast-enhanced ultrasound, for further characterisation of small renal masses, tumour thrombus and differentiation of unclear renal masses, in case the results of contrast-enhanced CT are indeterminate.	Strong
Offer brain CT/MRI in metastatic patients when systemic therapy or cytoreductive nephrectomy is considered.	Weak

Do not routinely use bone scan and/or positron-emission tomography CT for staging of renal cell carcinoma.	Weak
Perform a renal tumour biopsy before ablative therapy and systemic therapy without previous pathology.	Strong
Perform a percutaneous biopsy in select patients who are considering active surveillance.	Weak
Use a coaxial technique when performing a renal tumour biopsy.	Strong
Do not perform a renal tumour biopsy of cystic renal masses unless a significant solid component is visible at imaging.	Strong
Use a core biopsy technique rather than fine needle aspiration for histological characterisation of solid renal tumours.	Strong

5.5 Summary of evidence and recommendations for genetic assessment of RCC

Summary of evidence	LE
Hereditary kidney cancer is thought to account for 5–8% of all kidney cancer cases, though that number is likely an underestimate.	3
In case of renal cancer, if patient's age is 46 years or younger, and/or with bilateral or multifocal tumours and/or with a first or second-degree relative with RCC and/or with close blood relative with a known pathogenic variant and/or with specific histologic characteristics (see text), the risk of hereditary cancer is significantly higher.	3
Hereditary RCC detection has unique implications for decision-making and follow-up.	3

Recommendations	Strength rating
Perform a genetic evaluation in patients aged ≤ 46 years, with bilateral or multifocal tumours and/or a first or second-degree relative with RCC and/or a close blood relative with a known pathogenic variant and/or specific histologic characteristics which suggest the presence of a hereditary form of RCC.	Strong
Refer patients to a cancer geneticist or to a comprehensive clinical care centre in case of suspected hereditary kidney cancer.	Strong

6. PROGNOSTIC FACTORS

6.1 Classification

Prognostic factors can be classified into: anatomical, histological, clinical, and molecular.

6.2 Anatomical factors

Tumour size, venous invasion and extension, collecting system invasion, perinephric- and sinus fat invasion, adrenal involvement, and LN and distant metastasis are included in the TNM classification system [174, 175] (Table 4.1).

6.3 Histological factors

Histological factors include tumour grade, RCC subtype, lymphovascular invasion, tumour necrosis, and invasion of the collecting system [176, 177]. Tumour grade is considered one of the most important histological prognostic factors. Fuhrman nuclear grade is based on simultaneous investigation of nuclear size, nuclear shape and nucleolar prominence [178]. It has been the most widely accepted grading system for several decades, but has now been largely replaced by the WHO/ISUP grading classification [179]. This relies solely on nucleolar prominence for grade 1-3 tumours, allowing for less inter-observer variation [180]. It has been shown that the WHO/ISUP grading provides superior prognostic information compared to Fuhrman grading, especially for grade 2 and grade 3 tumours [181]. Rhabdoid and sarcomatoid changes can be found in all RCC types and are equivalent to grade 4 tumours. Sarcomatoid changes are more often found in chRCC than other subtypes [182]. The percentage of the sarcomatoid component appears to be prognostic as well, with a larger percentage of involvement being associated with worse survival. However, there is no agreement on the optimal prognostic cut-off for sub-classifying sarcomatoid changes [183, 184]. The WHO/ISUP grading system is applicable to both ccRCC and pRCC. It is currently not recommended to grade chRCC. However,

a recent study suggested a two-tiered chRCC grading system (low vs. high grade) based on the presence of sarcomatoid differentiation and/or tumour necrosis, which was statistically significant on multivariable analysis [185]. Both the WHO/ISUP and chRCC grading systems need to be validated for prognostic systems and nomograms [179].

Renal cell carcinoma subtype is regarded as another important prognostic factor. On univariable analysis, patients with chRCC vs. pRCC vs. ccRCC had a better prognosis [186, 187] (Table 6.1). However, prognostic information provided by the RCC type is lost when stratified according to tumour stage [187, 188] (LE: 3).

In a recent cohort study of 1,943 patients with ccRCC and pRCC significant survival differences were only shown between pRCC type I and ccRCC [189]. Papillary RCC has been traditionally divided into type 1 and 2, but a subset of tumours shows mixed features. For more details, see Section 3.2 – Histological diagnosis. Data also suggest that type 2 pRCC is a heterogeneous entity with multiple molecular subgroups [27]. Some studies suggest poorer survival for type 2 than type 1 [190], but this association is often lost in the multivariable analysis [191]. A meta-analysis did not show a significant survival difference between both types [192, 193].

Renal cell carcinoma with Xp11.2 translocation has a poor prognosis [194]. Its incidence is low, but its presence should be systematically assessed in young patients. Renal cell carcinoma type classification has been confirmed by cytogenetic and genetic analyses [195-197] (LE: 2b). Surgically excised malignant complex cystic masses contain ccRCC in the majority of cases, and more than 80% are pT1. In a recent series, five-year CSS was 98% [198]. Differences in tumour stage, grade and CSS between RCC types are illustrated in Table 6.1.

Table 6.1: Baseline characteristics and cancer-specific survival of surgically treated patients by RCC type [162]

Survival time	% RCC	% Sarcomatoid	% T3-4	% N1	% M1	% 10 year CSS (%)
Clear-cell RCC	80	5	33	5	15	62
Papillary RCC	15	1	11	5	3	86
Chromophobe RCC	5	8	15	4	4	86

CSS = cancer-specific survival.

In all RCC types, prognosis worsens with stage and histopathological grade (Table 6.2). The five-year OS for all types of RCC is 49%, which has improved since 2006, probably due to an increase in incidentally detected RCCs and new systemic treatments [199, 200]. Although not considered in the current N classification, the number of metastatic regional LNs is an important predictor of survival in patients without distant metastases [201].

Table 6.2: Cancer-specific survival by stage [20]

Grade	HR (95% CI)
T1N0M0	Referent
T2N0M0	2.71 (2.17–3.39)
T3N0M0	5.20 (4.36–6.21)
T4N0M0	16.88 (12.40–22.98)
N+M0	16.33 (12.89–20.73)
M+	33.23 (28.18–39.18)

CI = confidence interval; HR = hazard ratio.

6.4 Clinical factors

Clinical factors include performance status (PS), local symptoms, cachexia, anaemia, platelet count, neutrophil count, lymphocyte count, C-reactive protein (CRP) [202], albumin, and various indices deriving from these factors such as the neutrophil-to-lymphocyte ratio (NLR) [100, 203-208] (LE: 3). As a marker of systemic inflammatory response, a high pre-operative NLR has been associated with poor prognosis [209], but there is significant heterogeneity in the data and no agreement on the optimal prognostic cut-off. Even though obesity is an aetiological factor for RCC, it has also been observed to provide prognostic information. A high body mass index (BMI) appears to be associated with improved survival outcomes in both non-metastatic and metastatic RCC [210-212]. This association is linear with regards to cancer-specific mortality, while obese RCC

patients show increasing all-cause mortality with increasing BMI [213]. There is also evolving evidence on the prognostic value of body composition indices measured on cross-sectional imaging, such as sarcopenia and fat accumulation [208, 214, 215].

6.5 Molecular factors

Numerous molecular markers such as carbonic anhydrase IX (CaIX), VEGF, hypoxia-inducible factor (HIF), Ki67 (proliferation), p53, p21 [216], PTEN (phosphatase and tensin homolog) cell cycle [217], E-cadherin, osteopontin [218] CD44 (cell adhesion) [219, 220], CXCR4 [221], PD-L1 [222], miRNA, SNPs, gene mutations, and gene methylations have been investigated (LE: 3) [25]. While the majority of these markers are associated with prognosis and many improve the discrimination of current prognostic models, there has been very little emphasis on external validation studies. Furthermore, there is no conclusive evidence on the value of molecular markers for treatment selection in mRCC [202, 222, 223]. Their routine use in clinical practice is therefore not recommended.

Several prognostic and predictive marker signatures have been described for specific systemic treatments in mRCC. In the JAVELIN Renal 101 trial (NCT02684006), a 26-gene immunomodulatory gene signature predicted PFS in those treated with avelumab plus axitinib, while an angiogenesis gene signature was associated with PFS for sunitinib. Mutational profiles and histocompatibility leukocyte antigen (HLA) types were also associated with PFS, while PD-L1 expression and tumour mutational burden were not [224]. In Immotion151 (NCT02420821), a T effector/IFN-γ-high or angiogenesis-low gene expression signature predicted improved PFS for atezolizumab plus bevacizumab compared to sunitinib. The angiogenesis-high gene expression signature correlated with longer PFS in patients treated with sunitinib [225]. In CheckMate 214 (NCT02231749), a higher angiogenesis gene signature score was associated with better overall response rates and PFS for sunitinib, while a lower angiogenesis score was associated with higher ORR in those treated with nivolumab plus ipilimumab. Progression-free survival ≥ 18 months was more often seen in patients with higher expression of Hallmark inflammatory response and Hallmark epithelial mesenchymal transition gene sets [208].

Urinary and plasma Kidney-Injury Molecule-1 (KIM-1) has been identified as a potential diagnostic and prognostic marker. KIM-1 concentrations were found to predict RCC up to five years prior to diagnosis and were associated with a shorter survival time [226]. KIM-1 is a glycoprotein marker of acute proximal tubular injury and therefore mainly expressed in RCC derived from the proximal tubules such as ccRCC and pRCC [227]. While early studies are promising, more high-quality research is required. Several retrospective studies and large molecular screening programs have identified mutated genes and chromosomal changes in ccRCC with distinct clinical outcomes. The expression of the *BAP1* and *PBRM1* genes, situated on chromosome 3p in a region that is deleted in more than 90% of ccRCCs, have shown to be independent prognostic factors for tumour recurrence [228-230]. These published reports suggest that patients with *BAP1*-mutant tumours have worse outcomes compared with patients with *PBRM1*-mutant tumours [229]. Loss of chromosome 9p and 14q have been consistently shown to be associated with poorer survival [231-233]. The TRACERx renal consortium has proposed a genetic classification based on RCC evolution (punctuated vs. branched vs. linear), which correlates with tumour aggressiveness and survival [232]. Additionally, a 16-gene signature was shown to predict disease-free survival (DFS) in patients with non-metastatic RCC [234]. However, these signatures have not been validated by independent researchers yet.

6.6 Prognostic models

Prognostic models combining independent prognostic factors have been developed and externally validated [235-241]. These models are more accurate than TNM stage or grade alone for predicting clinically relevant oncological outcomes (LE: 3). Before being adopted, new prognostic models should be evaluated and compared to current prognostic models with regards to discrimination, calibration and net benefit. In metastatic disease, risk groups assigned by the Memorial Sloan Kettering Cancer Center (MSKCC) (primarily created in the pre-targeted therapy, and validated in patients receiving targeted therapy) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (initially created in the targeted therapy era) differ in 23% of cases [242]. The IMDC model has been used in the majority of recent randomised trials, including those with immune checkpoint inhibitors (ICIs), and may therefore be the preferred model for clinical practice. The discrimination of the IMDC model may be improved by addition of a seventh variable, namely presence of brain, bone, and/or liver metastases [243]. IMDC intermediate risk disease may also be sub-classified according to presence of bone metastasis or by platelet count [244, 245]. There is no conclusive evidence that one prognostic model is more accurate than another. Tables 6.3 and 6.4 summarise the current most relevant prognostic models.

6.7 Summary of evidence and recommendations for prognostic factors

Summary of evidence	LE
In RCC patients, TNM stage, tumour size, grade, and RCC subtype provide important prognostic information.	2a

Recommendations	Strength rating
Use the current Tumour, Node, Metastasis classification system.	Strong
Use the WHO/ISUP grading system and classify renal cell carcinoma type.	Strong
Use prognostic models in localised and metastatic disease.	Strong
Do not routinely use molecular markers to assess prognosis.	Strong

Table 6.3: Prognostic models for localised RCC

Prognostic model	Subtype*	Risk factors/prognostic factors
UISS** [246]	All	1. ECOG PS 2. T classification 3. N classification (N+ classified as metastatic) 4. Grade T1N0M0G1–2, ECOG PS 0: low-risk disease T3N0M0G2–4, ECOG PS ≥ 1 OR T4N0M0: high-risk disease Any other N0M0: intermediate-risk disease
Leibovich score/model 2003 [238]	CC	1. T classification (pT1a: 0, pT1b: 1, pT2:3, pT3-4: 4 points) 2. N classification (pNx/N0: 0, pN+: 2 points) 3. Tumour size (< 10 cm: 0, ≥ 10 cm: 1 point) 4. Grade (G1-2: 0, G3: 1, G4: 3 points) 5. Tumour necrosis (absent: 0, present: 1 point) 0–2 points: low-risk disease 3–5 points: intermediate-risk disease 6 or more points: high-risk disease
Leibovich score/model 2018 [247]	CC, P, CH	ccRCC • Progression (9 factors): constitutional symptoms, grade, tumour necrosis, sarcomatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus level, extension beyond kidney, nodal involvement. • Cancer-specific survival (12 factors): age, ECOG PS, constitutional symptoms, adrenalectomy, surgical margins, grade, tumour necrosis, sarcomatoid features, tumour size, perinephric or sinus fat invasion, tumour thrombus, nodal involvement. • No risk groups/prognostic groups. pRCC • Low risk (group 1): grade 1–2, no fat invasion, no tumour thrombus. • Intermediate risk (group 2): grade 3, no fat invasion, no tumour thrombus. • High risk (group 3): grade 4 or fat invasion or any level tumour thrombus. chRCC • Low risk (group 1): no fat invasion, no sarcomatoid differentiation, no nodal involvement. • Intermediate risk (group 2): fat invasion and no sarcomatoid differentiation and no nodal involvement. • High risk (group 3): sarcomatoid differentiation or nodal involvement.

VENUSS score/model*** [191]	P	1. T classification (pT1: 0, pT2: 1, pT3-4: 2 points) 2. N classification (pNx/pN0: 0, pN1: 3 points) 3. Tumour size (≤ 4 cm: 0, > 4 cm: 2 points) 4. Grade (G1/2: 0, G3/4: 2 points) 5. Tumour thrombus (absent: 0, present: 2 points) 0–2 points: low-risk disease 3–5 points: intermediate-risk disease 6 or more points: high-risk disease
GRANT score/model**** [248]	All	1. Age > 60 years 2. T classification = T3b, pT3c or pT4 3. N classification = pN1 4. (Fuhrman) grade = G3 or G4 0–1 factors: favourable-risk disease 2 or more factors: unfavourable-risk disease

* *ccRCC = clear-cell RCC; ECOG = Eastern Cooperative Oncology Group; pRCC = papillary RCC; chRCC = chromophobe RCC; PS = performance status.*

** *University of California Integrated Staging system. Available at https://www.mdcalc.com/ucla-integrated-staging-system-uiss-renal-cell-carcinoma-rcc.*

*** *Venous extension, Nuclear grade, Size, Stage. Available at https://www.evidencio.com/models/show/2369.*

**** *Grade, Age, Nodes and Tumour.*

Table 6.4: Prognostic models for metastatic RCCC

Prognostic model	Subtype	Risk factors/prognostic factors
MSKCC [249]**	All	1. Karnofsky PS [250]* < 80% 2. Interval from diagnosis to systemic treatment < 1 year 3. Haemoglobin < lower limit of normal 4. Corrected calcium >10 mg/dL/> 2.5 mmol/L 5. LDH > 1.5x upper limit of normal 0 factors: favourable-risk disease 1–2 factors: intermediate-risk disease 3–5 factors: poor-risk disease
IMDC [251]***	All	1. Karnofsky PS [250]* < 80% 2. Interval from diagnosis to treatment < 1 year 3. Haemoglobin < lower limit of normal 4. Corrected calcium > upper limit of normal (i.e., > 10.2 mg/dL) 5. Neutrophil count > upper limit of normal (i.e., > 7.0×10^9/L) 6. Platelet count > upper limit of normal (i.e., > 400,000) 0 factors: favourable-risk disease 1–2 factors: intermediate-risk disease 3–6 factors: poor-risk disease

IMDC = International Metastatic Renal Cancer Database Consortium; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; PS = performance status.

* *Karnofsky performance status calculator: https://www.thecalculator.co/health/Karnofsky-Score-for-Performance-Status-Calculator-961.html.*

** *MSKCC: https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-etastaticrenal-cell-carcinoma-rcc.*

*** *IMDC: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-score-rcc.*

7. DISEASE MANAGEMENT

7.1 Treatment of localised RCC

*7.1.1 **Introduction***

Sections 7.1.2 and 7.2.4.2 are underpinned by a systematic review which includes all relevant published literature comparing surgical management of localised RCC (T1-2N0M0). Randomised or quasi-RCTs were included. However, due to the very limited number of RCTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective matched-pair studies, and comparative studies from the databases of well-defined registries were also included. Historically, surgery has been the benchmark for the treatment of localised RCC.

*7.1.2 **Surgical treatment***

7.1.2.1 Nephron-sparing surgery versus radical nephrectomy in localised RCC

7.1.2.1.1 T1 RCC

Outcome 1: Cancer-specific survival

Most studies comparing the oncological outcomes of PN and RN are retrospective and include cohorts of varied and, overall, limited size [252, 253]. There is only one, prematurely closed, prospective RCT including patients with organ-confined RCCs of limited size (< 5 cm), showing comparable non-inferiority of CSS for PN vs. RN (HR: 2.06 [95% CI: 0.62–6.84]) [254].

Outcomes 2 & 3: Overall mortality and renal function

Partial nephrectomy preserved kidney function better after surgery, thereby potentially lowering the risk of development of cardiovascular disorders [252, 255-259]. When compared with a radical surgical approach, several retrospective analyses of large databases have suggested a decreased cardiovascular-specific mortality [256, 260] as well as improved OS for PN compared to RN. However, in some series this held true only for younger patients and/or patients without significant comorbidity at the time of the surgical intervention [261, 262]. An analysis of the U.S. Medicare database [263] could not demonstrate an OS benefit for patients ≥ 75 years of age when RN or PN were compared with non-surgical management.

Conversely, another series that addressed this question and also included Medicare patients, suggested an OS benefit in older patients (75–80 years) when subjected to surgery rather than non-surgical management. Shuch *et al.* compared patients who underwent PN for RCC with a non-cancer healthy control group via a retrospective database analysis; showing an OS benefit for the cancer cohort [264]. These conflicting results may be an indication that unknown statistical confounders hamper the retrospective analysis of population-based tumour registries. In the only prospectively randomised, but prematurely closed, heavily underpowered, trial, PN seems to be less effective than RN in terms of OS in the intention to treat (ITT) population (HR: 1.50 [95% CI: 1.03–2.16]). However, in the targeted RCC population of the only RCT, the trend in favour of RN was no longer significant [254]. Taken together, the OS advantage suggested for PN vs. RN remains an unresolved issue.

Patients with a normal pre-operative renal function and a decreased GFR due to surgical treatment (either RN or PN), generally present with stable long-term renal function [259]. Adverse OS in patients with a pre-existing GFR reduction does not seem to result from further renal function impairment following surgery, but rather from other medical comorbidities causing pre-surgical chronic kidney disease (CKD) [265]. However, in particular in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of development of ESRD which requires haemodialysis. Huang *et al.* found that 26% of patients with newly diagnosed RCC had an GFR ≤ 60 mL/min, even though their baseline serum creatinine levels were in the normal range [103].

Outcomes 4 & 5: Peri-operative outcomes and quality of life

In terms of the intra- and peri-operative morbidity/complications associated with PN vs. RN, the European Organisation for Research and Treatment of Cancer (EORTC) randomised trial showed that PN for small, easily resectable, incidentally discovered RCC, in the presence of a normal contralateral kidney, can be performed safely with slightly higher complication rates than after RN [266].

Only a limited number of studies are available addressing quality of life (QoL) following PN vs. RN, irrespective of the surgical approach used (open vs. minimally invasive). Quality of life was ranked higher following PN as compared to RN, but in general patients' health status deteriorated following both approaches [266, 267].

In view of the above, and since oncological safety (CSS and RFS) of PN, so far, has been found non-differing from RN outcomes, PN is the treatment of choice for T1 RCC since it preserves kidney function better and in the long term potentially limits the incidence of cardiovascular disorders. Whether decreased mortality from

any cause can be attributed to PN is still unresolved, but in patients with pre-existing CKD, PN is the preferred surgical treatment option as it avoids further deterioration of kidney function; the latter being associated with a higher risk of development of ESRD and the need for haemodialysis. Irrespective of the available data, in frail patients, treatment decisions should be individualised, weighing the risks and benefits of PN vs. RN, the increased risk of peri-operative complications and the risk of developing or worsening CKD post-operatively.

7.1.2.1.2 T2 RCC

There is very limited evidence on the optimal surgical treatment for patients with larger renal masses (T2). Some retrospective comparative studies of PN vs. RN for T2 RCC have been published [268]. A trend for lower tumour recurrence- and cancer-specific mortality is reported in PN groups. The estimated blood loss is reported to be higher for PN groups, as is the likelihood of post-operative complications [268]. A recent multicentre study compared the survival outcomes in patients with larger (≥ 7 cm) ccRCC treated with PN vs. RN with long-term follow-up (median 102 months). Compared to the RN group, the PN group had a significantly longer median OS (p = 0.014) and median CSS (p = 0.04) [269]. Retrospective comparative studies of cT1 and cT2 RCC patients upstaged to pT3a RCC show contradictory results: some reports suggest similar oncologic outcomes between PN and RN [270], whilst another recent report suggests that PN of clinical T1 in pathologically upstaged pT3a of cT1 RCC is associated with a significantly shorter recurrence-free survival than RN [271]. Overall the level of the evidence is low. These studies including T2 masses all have a high risk of selection bias due to imbalance between the PN and RN groups regarding patient's age, comorbidities, tumour size, stage, and tumour position. These imbalances in covariation factors may have a greater impact on patient outcome than the choice of PN or RN. The Panel's confidence in the results is limited and the true effects may be substantially different.

In view of the above, the risks and benefits of PN should be discussed with patients with T2 tumours. In this setting PN should be considered, if technically feasible, in patients with a solitary kidney, bilateral renal tumours or CKD with sufficient parenchymal volume preserved to allow sufficient post-operative renal function.

7.1.2.1.3 T3 RCC

A recent meta-analysis of nine articles including 1,278 patients with PN and 2,113 patients with RN in pT3a RCC showed no difference in CSS, OS, CSM and RFS, indicating that PN techniques can be used for functional benefits and if technically feasible [272].

7.1.2.2 Associated procedures

7.1.2.2.1 Adrenalectomy

One prospective non-randomised study compared the outcomes of RN with or without, ipsilateral adrenalectomy [273]. Multivariable analysis showed that upper pole location was not predictive of adrenal involvement, but tumour size was. No difference in OS at five or ten years was seen with, or without, adrenalectomy. Adrenalectomy was justified using criteria based on radiographic- and intra-operative findings. Only 48 of 2,065 patients underwent concurrent ipsilateral adrenalectomy of which 42 of the 48 interventions were for benign lesions [273].

7.1.2.2.2 Lymph node dissection for clinically negative lymph nodes (cN0)

The indication for LN dissection (LND) together with PN or RN is still controversial [274]. The clinical assessment of LN status is based on the detection of an enlargement of LNs either by CT/MRI or intra-operative palpability of enlarged nodes. Less than 20% of suspected metastatic nodes (cN+) are positive for metastatic disease at histopathological examination (pN+) [275]. Both CT and MRI are unsuitable for detecting malignant disease in nodes of normal shape and size [276]. For clinically positive LNs (cN+) see Section 7.2.2.

Smaller retrospective studies have suggested a clinical benefit associated with a more or less extensive LND preferably in patients at high risk for lymphogenic spread. In a large retrospective study, the outcomes of RN, with or without LND, in patients with high-risk non-mRCC were compared using a propensity score analysis. In this study LND was not significantly associated with a reduced risk of distant metastases, cancer-specific or all-cause mortality. The extent of the LND was not associated with improved oncologic outcomes [277]. The number of LN metastases (< / > 4) as well as the intra- and extracapsular extension of intra-nodal metastasis correlated with the patients´ clinical prognosis in some studies [276, 278-280]. Better survival outcomes were seen in patients with a low number of positive LNs (< 4) and no extranodal extension. On the basis of a retrospective Surveillance, Epidemiology and End Results (SEER) database analysis of > 9,000 patients no effects of an extended LND (eLND) on the disease-specific survival (DSS) of patients with pathologically confined negative nodes was demonstrated [281]. However, in patients with pathologically proven lymphogenic spread (pN+), an increase of 10 for the number of nodes dissected resulted in a 10% absolute increase in DSS.

In addition, in a larger cohort of 1,983 patients, Capitanio *et al.* demonstrated that eLND results in a significant prolongation of CSS in patients with unfavourable prognostic features (e.g., sarcomatoid differentiation, large tumour size) [282]. As to morbidity related to eLND, a recent retrospective propensity score analysis from a large single-centre database showed that eLND is not associated with an increased risk of Clavien grade ≥ 3 complications. Furthermore, LND was not associated with length of hospital stay or estimated blood loss [283].

Only one prospective RCT evaluating the clinical value of LND combined with surgical treatment of primary RCC has been published so far. With an incidence of LN involvement of only 4%, the risk of lymphatic spread appears to be very low. Recognising the latter, only a staging effect was attributed to LND [275]. This trial included a very high percentage of patients with pT2 tumours, which are not at increased risk for LN metastases. Only 25% of patients with pT3 tumours underwent a complete LND and the LN template used by the authors was not clearly stated.

The optimal extent of LND remains controversial. Retrospective studies suggest that an eLND should involve the LNs surrounding the ipsilateral great vessel and the inter-aortocaval region from the crus of the diaphragm to the common iliac artery. Involvement of inter-aortocaval LNs without regional hilar involvement is reported in up to 35–45% of cases [276, 284, 285]. At least fifteen LNs should be removed [282, 286]. Sentinel LND is an investigational technique [287, 288].

7.1.2.2.3 Embolisation

Before routine nephrectomy, tumour embolisation has no benefit [289, 290]. In patients unfit for surgery, or with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [291, 292]. These indications will be revisited in Sections 7.2 and 7.3 with cross reference to the summary of evidence and recommendations below.

7.1.2.2.4 Summary of evidence and recommendations for the treatment of localised RCC

Summary of evidence	**LE**
The oncological outcome in terms of OS following PN equals that of RN in patients with c/p T1 RCC.	1b
Retrospective studies suggest that oncological outcomes are similar following PN vs. RN in patients with larger (≥ 7 cm) RCC. Post-operative complication rates are higher in PN patients.	3b
Ipsilateral adrenalectomy during RN or PN has no survival advantage in the absence of clinically evident adrenal involvement.	3
In patients with localised disease without radiographic evidence of LN metastases, a survival advantage of LND in conjunction with RN is not demonstrated in randomised trials.	2b
Retrospective studies suggest a clinical benefit associated with lymphadenectomy in high-risk patients.	2b
In patients unfit for surgery with massive haematuria or flank pain, embolisation can be a beneficial palliative approach.	3

Recommendations	**Strength rating**
Offer surgery to achieve cure in localised renal cell cancer.	Strong
Offer partial nephrectomy (PN) to patients with T1 tumours.	Strong
Offer PN to patients with T2 tumours and a solitary kidney or chronic kidney disease, if technically feasible.	Weak
Do not perform ipsilateral adrenalectomy if there is no clinical evidence of invasion of the adrenal gland.	Strong
Do not offer an extended lymph node dissection to patients with organ-confined disease.	Weak
Offer embolisation to patients unfit for surgery presenting with massive haematuria or flank pain.	Weak

*7.1.3 **Radical and partial nephrectomy techniques***

7.1.3.1 Radical nephrectomy techniques

No RCTs have assessed the oncological outcomes of laparoscopic vs. open RN. A cohort study [293] and retrospective database reviews are available, mostly of low methodological quality, showing similar oncological outcomes even for higher stage disease and locally more advanced tumours [294-296]. Based on a systematic review, less morbidity was found for laparoscopic vs. open RN [252].

Data from one RCT [268] and two non-randomised studies [297, 298] showed a significantly shorter hospital stay and lower analgesic requirement for the laparoscopic RN group as compared with the open group. Convalescence time was also significantly shorter [298]. No difference in the number of

patients receiving blood transfusions was observed, but peri-operative blood loss was significantly less in the laparoscopic arm in all three studies [295, 297, 298]. Surgical complication rates were low with very wide confidence intervals. There was no difference in complications, but operation time was significantly shorter in the open nephrectomy arm. Post-operative QoL scores were similar [297].

Some comparative studies focused on the peri-operative outcomes of laparoscopic vs. RN for renal ≥ T2 tumours. Overall, patients who underwent laparoscopic RN were shown to have lower estimated blood loss, less post-operative pain, shorter length of hospital stay and convalescence compared to those who underwent open RN [296, 298, 299]. Intra-operative and post-operative complications were similar in the two groups and no significant differences in CSS, PFS and OS were reported [296, 298, 299] (LE: 2b). Another multicentre propensity matched analysis compared laparoscopic- and open surgery for pT3a RCC, showing no significant difference in three-year RFS between groups [300]. The best approach for laparoscopic RN was the retroperitoneal or transperitoneal approach with similar oncological outcomes in two RTCs [301, 302] and one quasi-randomised study [276]. Quality of life variables were similar for both approaches. Hand-assisted vs. standard laparoscopic RN was compared in one quasi-randomised study [303] and one database review and estimated five-year OS, CSS, and RFS rates were comparable [304]. Duration of surgery was significantly shorter in the hand-assisted approach, while length of hospital stay and time to non-strenuous activities were shorter for the standard laparoscopic RN cohort [303, 304]. However, the sample size was small.

Data of a large retrospective cohort study on robot-assisted laparoscopic vs. laparoscopic RN showed robot-assisted laparoscopic RN was not associated with increased risk of any or major complications but had a longer operating time and higher hospital costs compared with laparoscopic RN [305]. A recent systematic review and meta-analysis of seven studies with 1,832 patients showed no difference between the two approaches in peri-operative outcomes, including operative time, blood loss, conversion rates and complications [306]. A systematic review reported on robot-assisted laparoscopic vs. conventional laparoscopic RN, showing no substantial differences in local recurrence rates, nor in all-cause cancer-specific mortality [307]. Similar results were seen in observational cohort studies comparing 'portless' and 3-port laparoscopic RN, with similar perioperative outcomes [308, 309].

7.1.3.2 Partial nephrectomy techniques

7.1.3.2.1 Open versus laparoscopic approach

Studies comparing laparoscopic and open PN found no difference in PFS [310-313] and OS [312, 313] in centres with laparoscopic expertise. However, the oncological safety of laparoscopic vs. open PN has, so far, only been addressed in studies with relatively limited follow-up [300]. However, the higher number of patients treated with open surgery in this series might reflect a selection bias by offering laparoscopic surgery in case of a less complex anatomy [300]. The mean estimated blood loss was found to be lower with the laparoscopic approach [310, 312, 314], while post-operative mortality, deep vein thrombosis, and pulmonary embolism events were similar [310, 312]. Operative time is generally longer with the laparoscopic approach [311-313] and warm ischaemia time is shorter with the open approach [310, 312, 314, 315]. In a matched-pair comparison, GFR decline was greater in the laparoscopic PN group in the immediate post-operative period [313], but not after 3.6 years follow-up. In another comparative study, the surgical approach was not an independent predictor for post-operative CKD [315]. Retroperitoneal and transperitoneal laparoscopic PN have similar peri-operative outcomes [316]. Simple tumour enucleation also had similar PFS and CSS rates compared to standard PN and RN in a large study [317]. The feasibility of laparo-endoscopic single-site PN has been shown in selected patients but larger studies are needed to confirm its safety and clinical role [318].

7.1.3.2.2 Open versus robotic approach

One study prospectively compared the peri-operative outcomes of a series of robot-assisted and open PN performed by the same experienced surgeon. Robot-assisted PN was superior to open PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischaemia time, operative time, immediate- early- and short-term complications, variation in creatinine levels and pathologic margins were similar between groups [319].

A multicentre French prospective database compared the outcomes of 1,800 patients who underwent open PN and robot-assisted PN. Although the follow-up was shorter, there was a decreased morbidity in the robot-assisted PN group with less overall complications, less major complications, less transfusions and a much shorter hospital stay [320].

7.1.3.2.3 Open versus hand-assisted approach

Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative study of open vs. HALPN showed no difference in OS or RFS at intermediate-term follow-up. The authors observed a lower rate of intra-operative and all-grade post-operative 30-day complications in HALPN vs. open PN patients, but there was no significant difference in high Clavien grade complications. Three months after the operation, GFR was lower in the HALPN than in the open PN group [321].

7.1.3.2.4 Open versus laparoscopic versus robotic approaches

In a retrospective propensity-score-matched study, comparing open-, laparoscopic- and robot-assisted PN, after five-year of median follow-up, similar rates of local recurrence, distant metastasis and cancer-related death rates were found [322].

7.1.3.2.5 Laparoscopic versus robotic approach

Another study included the 50 last patients having undergone laparoscopic and robotic PN for T1-T2 renal tumours by two different surgeons with an experience of over 200 procedures each in laparoscopic and robotic PN and robot-assisted partial nephrectomy (RAPN), respectively, at the beginning of the study. Peri-operative and short-term oncological and functional outcomes appeared broadly comparable between RAPN and LPN when performed by highly experienced surgeons [323].

A meta-analysis, including a series of NSS with variable methodological quality compared the peri-operative outcomes of robot-assisted- and laparoscopic PN. The robotic group had a significantly lower rate of conversion to open surgery and to radical surgery, shorter warm ischaemia time, smaller change in estimated GFR after surgery and shorter length of hospital stay. No significant differences were observed between the two groups regarding complications, change of serum creatinine after surgery, operative time, estimated blood loss and positive surgical margins [324].

A recent multi-institutional prospective study of 105 patients with hilar tumours demonstrated a reduced warm ischaemia time (20.2 min vs. 27.7 min) and a comparable PSM rate of 1.9% when compared with a historical laparoscopic control group which was defined by literature research and meta-analysis for warm ischaemia time and PSM, respectively [325].

7.1.3.2.6 Laparoscopic transperitoneal versus retroperitoneal approach

Data from the Italian RECORD 2 project, a multi-institutional prospective observational project, compared the transperitoneal vs. the retroperitoneal approach for laparoscopic PN. After propensity score matching (each group n = 413) no differences in post-operative complications (surgical and medical), positive surgical margins, early and late eGFR levels were observed. Intra-operative and surgical complications were slightly higher and operative times lower in the transperitoneal vs. the retroperitoneal approach [326].

7.1.3.2.7 Surgical volume

In a recent analysis of 8,753 patients who underwent PN, an inverse non-linear relationship of hospital volume with morbidity of PN was observed, with a plateauing seen at 35 to 40 cases per year overall, and 18 to 20 cases for the robotic approach [327]. A retrospective study of a U.S. National Cancer Database looked at the prognostic impact of hospital volume and the outcomes of robot-assisted PN, including 18,724 cases. This study shows that undergoing RAPN at higher-volume hospitals may have better peri-operative outcomes (conversion to open and length of hospital stay) and lower positive surgical margin rates [328]. A French study, including 1,222 RAPN patients, has shown that hospital volume is the main predictive factor of Trifecta achievement (no complications, warm ischaemia time < 25 min, and negative surgical margins) after adjustment for other variables, including surgeon volume [329]. The prospective Registry of Conservative and Radical Surgery for cortical renal tumour Disease (RECORd-2) study including 2,076 patients showed that the hospital volume (> 60 PN/year) is an independent predictor for positive surgical margins [330].

7.1.3.2.8 Pre-operative embolisation prior to partial nephrectomy

A systematic review and meta-analysis of 270 patients demonstrated significantly reduced blood loss in patients with selective renal artery embolisation (n = 222; 154 ± 22.6 mL vs. n = 48; 353.4 ± 69.6 mL) prior to partial nephrectomy [331].

7.1.3.3 Positive surgical margins on histopathological specimens

A positive surgical margin is encountered in about 2–8% of PNs [324]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [332, 333]. Most trials showed that intra-operative frozen section analysis had no influence on the risk of definite positive surgical margins [334]. A positive surgical margin status occurs more frequently in cases in which surgery is imperative (solitary kidneys and bilateral tumours) and in patients with adverse pathological features (pT2a, pT3a, grade III-IV) [335-338]. The potential negative impact of a positive margin status on the oncologic outcome is still controversial [332].

The majority of retrospective analyses reported so far indicated that positive surgical margins do not translate into a higher risk of metastases or a decreased CSS [336, 337]. On the other hand, another retrospective study of a large single institutional series showed that positive surgical margins are an independent predictor of PFS

due to a higher incidence of distant and local relapses [339]. Another retrospective study of 42,114 PN patients with 2,823 PSM patients (6.7%) showed an increased presence of PSM in upstaged pT3a tumours (14.1%), increased all-cause mortality in PSM patients and a decreased five-year OS rate in pT3a tumours (PSM: 69% vs. NSM: 90.9 %) [340].

However, only a proportion of patients with an uncertain margin status actually harbour residual malignancy [341]. Local tumour bed recurrences were found in 16% in patients with positive surgical margins compared with 3% in those with negative margins [335], Therefore, RN or re-resection of margins can result in over-treatment in many cases. Patients with positive surgical margins should be informed that they will need a more intense surveillance (imaging) follow-up and that they are at increased risk of secondary local therapies [336, 342]. On the other hand, protection from recurrence is not ensured by negative surgical margins [343].

7.1.3.4 Summary of evidence and recommendations for radical and partial nephrectomy techniques

Summary of evidence	**LE**
Laparoscopic RN has lower morbidity than open nephrectomy.	1b
Short-term oncological outcomes for T1-T2a tumours are equivalent for laparoscopic and open RN.	2a
Partial nephrectomy can be performed, either by open-, pure laparoscopic- or robot-assisted approach, based on surgeon's expertise and skills.	2b
Robot-assisted and laparoscopic PN are associated with shorter length of hospital stay and lower blood loss compared to open PN.	2b
Partial nephrectomy is associated with a higher percentage of positive surgical margins compared to RN.	3
Transperitoneal and retroperitoneal laparoscopic PN do not differ in in post-operative surgical and medical complications, positive surgical margins and kidney function.	2a
Hospital volume for PN might impact on surgical complications, warm ischaemia time and surgical margins.	3
Radical nephrectomy for positive surgical margins after PN can result in over-treatment in many cases.	3

Recommendations	**Strength rating**
Offer laparoscopic radical nephrectomy (RN) to patients with T2 tumours and localised masses not treatable by partial nephrectomy (PN).	Strong
Do not perform minimally invasive RN in patients with T1 tumours for whom a PN is feasible by any approach, including open.	Strong
Do not perform minimally invasive surgery if this approach may compromise oncological, functional, and peri-operative outcomes.	Strong
Intensify follow-up in patients with a positive surgical margin, especially in upstaged pT3a patients.	Weak

*7.1.4 **Therapeutic approaches as alternatives to surgery***

7.1.4.1 Surgical versus non-surgical treatment

Population-based studies compared the oncological outcomes of surgery (RN or PN) and non-surgical management for tumours < 4 cm. The analyses showed a significantly lower cancer-specific mortality in patients treated with surgery [263, 344, 345]. However, the patients assigned to the surveillance arm were older and likely to be frailer and less suitable for surgery. Other-cause mortality rates in the non-surgical group significantly exceeded that of the surgical group [344]. Analyses of older patients (> 75 years) failed to show the same benefit in cancer-specific mortality for surgical treatment [346-348].

7.1.4.2 Active surveillance and watchful waiting

Elderly and comorbid patients with incidental small renal masses have a low RCC-specific mortality and significant competing-cause mortality [349, 350]. Active surveillance is defined as the initial monitoring of tumour size by serial abdominal imaging (US, CT, or MRI) with delayed intervention reserved for tumours showing clinical progression during follow-up [351]. The concept of AS differs from the concept of watchful waiting; watchful waiting is reserved for patients whose comorbidities contraindicate any subsequent active treatment and do not require follow-up imaging, unless clinically indicated.

In the largest reported series of AS the growth of renal tumours was low and progression to metastatic disease was reported in only a limited number of patients [352, 353].

A single-institutional comparative study evaluating patients aged > 75 years showed decreased OS for those who underwent surveillance and nephrectomy relative to NSS for clinically T1 renal tumours. However, at multivariate analysis, management type was not associated with OS after adjusting for age, comorbidities, and other variables [349]. No statistically significant differences in OS and CSS were observed in

another study of RN vs. PN vs. AS for T1a renal masses with a follow-up of 34 months [354]. The prospective non-randomised multi-institutional Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) study enrolled 497 patients with solid renal masses < 4 cm who selected either AS or primary active intervention. Patients who selected AS were older, had worse ECOG scores, more comorbidities, smaller tumours, and more often had multiple and bilateral lesions. In patients who elected AS in this study the overall median small renal mass growth rate was 0.09 cm/year with a median follow-up of 1.83 years. The growth rate and variability decreased with longer follow-up. No patients developed metastatic disease or died of RCC [355, 356].

Overall survival for primary intervention and AS was 98% and 96% at two years, and 92% and 75% at five years, respectively (p = 0.06). At five years, CSS was 99% and 100%, respectively (p = 0.3). Active surveillance was not predictive of OS or CSS in regression modelling with relatively short follow-up [355]. Overall, both short- and intermediate-term oncological outcomes indicate that in selected patients with advanced age and/or comorbidities, AS is appropriate for initially monitoring of small renal masses, followed, if required, by treatment for progression [351-353, 357-360].

A multicentre study assessed QoL of patients undergoing immediate intervention vs. AS. Patients undergoing immediate intervention had higher QoL scores at baseline, specifically for physical health. The perceived benefit in physical health persisted for at least one year following intervention. Mental health, which includes domains of depression and anxiety, was not adversely affected while on AS [361].

In 136 biopsy-proven small renal mass (SRM) RCCs managed by AS median follow-up for patients who remained on AS was 5.8 years (interquartile range 3.4-7.5 years). Clear cell RCC grew faster than papillary type 1 SRMs (0.25 and 0.02 cm/year on average, respectively, p = 0.0003). Overall, 60 (44.1 %) of the malignant SRM progressed: 49 (82%) by rapid growth (volume doubling), seven (12%) increasing to ≥ 4 cm, and four (6.7%) by both criteria. Six patients developed metastases, and all were of ccRCC histology [362].

7.1.4.3 Role of renal tumour biopsy before active surveillance

Histological characterisation of small renal masses by renal tumour biopsy is useful to select tumours at lower risk of progression based on grade and histotype, which can be safely managed with AS. Pathology can also help to tailor surveillance imaging schedules. In the largest cohort of biopsy-proven, small, sporadic RCCs followed with AS, a significant difference in growth and progression among different RCC subtypes was observed. Clear-cell RCC small renal masses grew faster than papillary type 1 small renal masses (0.25 and 0.02 cm/year on average, respectively, p = 0.0003) [362].

7.1.4.4 Tumour ablation

7.1.4.4.1 Role of renal mass biopsy

A RMB is required prior to tumour ablation (TA) (see Sections 5.3 Renal tumour biopsy and 5.4 Summary of evidence and recommendations for the diagnostic assessment of RCC). Historically, up to 45% of patients underwent TA of a benign or non-diagnostic mass [363, 364]. A RMB in a separate session reduces over-treatment significantly, with 80% of patients with benign lesions opting not to proceed with TA [364]. Additionally, there is some evidence that the oncological outcome following TA differs according to RCC subtype which should therefore be factored into the decision-making process. In a series of 229 patients with cT1a tumours (mean size 2.5 cm) treated with RFA, the five-year DFS rate was 90% for ccRCC and 100% for pRCC (80 months: 100% vs. 87%, p = 0.04) [365]. In another series, the total TA effectiveness rate was 90.9% for ccRCC and 100% for pRCC [366]. A study comparing RFA with surgery suggested worse outcomes of RFA vs. PN in cT1b ccRCC, while no difference was seen in those with non-ccRCC [367]. Furthermore, patients with high-grade RCC or metastasis may choose different treatments over TA. Finally, patients without biopsy or a non-diagnostic biopsy are often assumed to have RCC and will undergo potentially unnecessary radiological follow-up or further treatment.

7.1.4.4.2 Cryoablation

Cryoablation is performed using either a percutaneous- or a laparoscopic-assisted approach, with technical success rates of > 95% [368]. In comparative studies, there was no significant difference in the overall complication rates between laparoscopic- and percutaneous cryoablation [369-371]. One comparative study reported similar OS, CSS, and RFS in 145 laparoscopic patients with a longer follow-up vs. 118 patients treated percutaneously with a shorter follow-up [370]. A shorter average length of hospital stay was found with the percutaneous technique [370-372]. A systematic review including 82 articles reported complication rates ranging between 8 and 20% with most complications being minor [373]. Although a precise definition of tumour recurrence is lacking, the authors reported a lower RFS as compared to that of PN.

Oncological outcomes after cryoablation have generally been favourable for cT1a tumours. In a recently published series of 308 patients with cT1a and cT1b tumours undergoing percutaneous cryoablation, local recurrence was seen in 7.7% of cT1a tumours vs. 34.5% of cT1b tumours. On multivariable regression, the risk

of disease progression increased by 32% with each 1 cm increase in tumour size (HR: 1.32, p < 0.001). Mean decline in eGFR was 11.7 mL/min/1.73 m^2 [374]. In another large series of 220 patients with biopsy proven cT1 RCC, five-year local RFS was 93.9%, while metastasis-free survival approached 94.4% [368]. A series of 134 patients with T1 RCC (median tumour size 2.8 cm) submitted to percutaneous cryoablation yielded a ten-year DSF of 94% [375].

For cT1b tumours, local tumour control rates drop significantly. One study showed local tumour control in only 60.3% at three years [376]. In another series, the PFS rate was 66.7% at twelve months [377]. Furthermore, recent analyses demonstrated five-year cancer-specific mortality rates of 7.6–9% [378, 379]. On multivariable analysis, cryoablation of cT1b tumours was associated a 2.5-fold increased risk of death from RCC compared with PN [378].

Recurrence after initial cryoablation is often managed with re-cryoablation, but only 45% of patients remain disease-free at two years [380].

7.1.4.4.3 Radiofrequency ablation

Radiofrequency ablation is performed laparoscopically or percutaneously. Several studies compared patients with cT1a tumours treated by laparoscopic or percutaneous RFA [381-384]. Complications occurred in up to 29% of patients but were mostly minor. Complication rates, recurrence rates and CSS were similar in patients treated laparoscopically and percutaneously.

The initial technical success rate on early (i.e., one month) imaging after one session of RFA is 94% for cT1a and 81% for cT1b tumours [385]. This is generally managed by re-RFA, approaching overall total technical success rates > 95% with one or more sessions [386].

Long-term outcomes with over five years of follow-up following RFA have been reported. In recent studies, the five-year OS rate was 73–79% [385, 386], due to patient selection. Oncological outcomes for cT1a tumours have been favourable. In a recent study, the ten-year disease-free survival rate was 82%, but there was a significant drop to 68% for tumours > 3 cm [386]. In series focusing on clinical T1b tumours (4.1–7.0 cm), the five-year DFS rate was 74.5% to 81% [385, 387]. Oncological outcomes appear to be worse than after surgery, but comparative data are severely biased (see Section 7.1.4.3.4). In general, most disease recurrences occur locally and recurrences beyond five years are rare [386, 387].

7.1.4.4.4 Tumour ablation versus surgery

The Guideline Panel performed a protocol-driven systematic review of comparative studies (including > 50 patients) of TA with PN for T1N0M0 renal masses [7]. Twenty-six non-randomised comparative studies published between 2000 and 2019 were included, recruiting a total of 16,780 patients. Four studies compared laparoscopic TA vs. laparoscopic/robotic PN; sixteen studies compared laparoscopic or percutaneous TA vs. open-, laparoscopic- or robotic PN; two studies compared different techniques of TA and four studies compared TA vs. PN vs RN. In this systematic review, TA as treatment for T1 renal masses was found to be safe in terms of complications and adverse events (AEs), but its long-term oncological effectiveness compared with PN remained unclear. The primary reason for the persisting uncertainty was related to the nature of the available data; most studies were retrospective observational studies with poorly matched controls, or single-arm case series with short follow-up. Many studies were poorly described and lacked a clear comparator. There was also considerable methodological heterogeneity. Another major limitation was the absence of clearly defined primary outcome measures. Even when a clear endpoint such as OS was reported, data were difficult to interpret because of the varying length and type of follow-up amongst studies. The Panel also appraised the published systematic reviews based on the AMSTAR 2 tool which showed critically low or low ratings [7].

Tumour ablation has been demonstrated to be associated with good long-term survival in several single-arm non-comparative studies [388, 389]. Due to the lack of controls, this apparent benefit is subject to significant uncertainties. Whether such benefit is due to the favourable natural history of such tumours or due to the therapeutic efficacy of TA, as compared to PN, remains unknown. In addition, there are data from comparative studies suggesting TA may be associated with worse oncological outcomes in terms of local recurrence and metastatic progression and cancer-specific mortality [261, 378, 379, 390, 391]. However, there appears to be no clinically significant difference in five-year cancer-specific mortality between TA and AS [345].

The Panel concluded that the current data are inadequate to reach conclusions regarding the clinical effectiveness of TA as compared with PN. Given these uncertainties in the presence of only low-quality evidence, TA can only be recommended to frail and/or comorbid patients with small renal masses.

7.1.4.4.5 Stereotactic ablative radiotherapy

Stereotactic ablative radiotherapy (SABR) has been emerging as a treatment option for medically inoperable patients with localised cT1a and cT1b tumours. Patients usually receive 26 Gy in a single fraction, three

fractions of 14 Gy or five fractions of 6 Gy [392, 393]. In a systematic review or non-comparative single-arm studies, the local control rate was 97.2% and the mean change in eGFR was 7.7 mL/min/1.73 m^2. Grade 3 or 4 toxicities occurred in 1.5% of patients. However, viable tumour cells are often seen in post-SABR biopsies, although their clinical significance remains unclear [393]. Although early results of SABR are encouraging, more evidence from randomised trials is needed.

7.1.4.4.6 Other ablative techniques

Some studies have shown the feasibility of other ablative techniques, such as microwave ablation, high-intensity focused US ablation and non-thermal irreversible electroporation. However, these techniques are still considered experimental. The best evidence base for these techniques exists for percutaneous microwave ablation. In a study of 185 patients with a median follow-up of 40 months, the five-year local progression rate was 3.2%, while 4.3% developed distant metastases [394]. Results appear to be favourable for cT1b tumours as well [395]. Overall, current data on cryoablation, RFA and microwave ablation of cT1a renal tumours indicate short-term equivalence with regards to complications, oncological and renal functional outcomes [396].

7.1.4.4.7 Summary of evidence and recommendation for therapeutic approaches as alternative to surgery

Summary of evidence	LE
Most population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management.	3
In AS cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1–2%).	3
Low-quality studies suggest high disease recurrence rates after RFA of tumours > 3 cm and after cryoablation of tumours > 4 cm.	3
Low-quality studies suggest a higher local recurrence rate for TA therapies compared to partial nephrectomy, but quality of data does not allow definitive conclusions.	3

Recommendations	Strength rating
Offer active surveillance (AS) or thermal ablation (TA) to frail and/or comorbid patients with small renal masses.	Weak
Perform a percutaneous renal mass biopsy prior to, and not concomitantly with TA.	Strong
When TA or AS are offered, discuss with patients about the harms/benefits with regards to oncological outcomes and complications.	Strong
Do not routinely offer TA for tumours > 3 cm and cryoablation for tumours > 4 cm.	Weak

7.2 Treatment of locally advanced RCC

*7.2.1 **Introduction***

In addition to the summary of evidence and recommendations outlined in Section 7.1 for localised RCC, certain therapeutic strategies arise in specific situations for locally advanced disease.

*7.2.2 **Role of lymph node invasion in locally advanced RCC***

In locally advanced RCC, the role of LND is still controversial. The only available RCT demonstrated no survival benefit for patients undergoing LND but this trial mainly included organ-confined disease cases [275]. In the setting of locally advanced disease, several papers addressed the topic with contradictory results, as did several systematic reviews. Bhindi *et al.* could not confirm any survival benefit in patients at high risk of progression treated with LND [397]. More recently, Luo *et al.* reported a systematic review and meta-analyses showing a survival benefit in patients with locally advanced disease treated with LND [398]. More specifically, thirteen studies on patients with LND and non-LND were identified and included in the analysis. In the subgroup of locally advanced RCC (cT3-T4NxM0), LND showed a significantly better OS rate in patients who had undergone LND compared to those without LND (HR: 0.73, 95% CI: 0.60–0.90, p = 0.003).

7.2.2.1 Management of clinically negative lymph nodes (cN-) in locally advanced RCC

In case of cN-, the probability of finding pathologically confirmed LN metastases ranges between 0 and 25%, depending mainly on primary tumour size and the presence of distant metastases [399]. In case of clinically negative LNs (cN-) at imaging, removal of LNs is justified only if visible or palpable during surgery [400], at least for staging, prognosis and follow-up implications although a benefit in terms of cancer control has not yet been demonstrated [277, 397]. Whether to extend the LND also to retroperitoneal areas without cN+ remains controversial [276].

7.2.2.2 Management of clinically positive lymph nodes (cN+) in locally advanced RCC

In case of cN+, the probability to find pathologically confirmed LN metastases ranges between 10.3% (cT1 tumours) up to 54.5% in case of locally advanced disease. In cN+, removal of visible and palpable nodes during lymphadenectomy is always justified [400], at least for staging, prognosis and follow-up implications, although a benefit in terms of cancer control has not yet been demonstrated [277, 397].

*7.2.3 **Management of locally advanced unresectable RCC***

In case of locally advanced unresectable RCC, a multi-disciplinary evaluation, including urologists, medical oncologists and radiation therapists is suggested to maximise cancer control, pain control and the best supportive care. In patients with non-resectable disease, embolisation can control symptoms, including visible haematuria or flank pain [291, 292, 401]. The use of systemic therapy to downsize tumours is experimental and cannot be recommended outside clinical trials.

*7.2.4 **Management of RCC with venous tumour thrombus***

Tumour thrombus formation in RCC patients is a significant adverse prognostic factor. Traditionally, patients with venous tumour thrombus undergo surgery to remove the kidney and tumour thrombus. Aggressive surgical resection is widely accepted as the default management option for patients with venous tumour thrombus [402-410].

7.2.4.1 The evidence base for surgery in patients with venous tumour thrombus

Data whether patients with venous tumour thrombus should undergo surgery is derived from case series only. In one of the largest published studies a higher level of thrombus was not associated with increased tumour dissemination to LNs, perinephric fat or distant metastasis [407]. Therefore, all patients with non-metastatic disease and venous tumour thrombus, and an acceptable PS, should be considered for surgical intervention, irrespective of the extent of tumour thrombus at presentation. The surgical technique and approach for each case should be selected based on the extent of tumour thrombus.

7.2.4.2 The evidence base for different surgical strategies

A systematic review was undertaken which included only comparative studies on the management of venous tumour thrombus in non-metastatic RCC [411, 412]. Only five studies were eligible for final inclusion, with a high risk of bias across all studies.

Minimal access techniques resulted in significantly shorter operating time compared with traditional median sternotomy [413-416].

The surgical method selected depended on the level of tumour thrombus and the grade of occlusion of the IVC [411, 413, 414, 417]. The relative benefits and harms of other strategies and approaches regarding access to the IVC and the role of IVC filters and bypass procedures remain uncertain.

7.2.4.3 Summary of evidence and recommendations for the management of RCC with venous tumour thrombus

Summary of evidence	**LE**
In patients with locally advanced disease, the survival benefit of LN dissection is unproven but LN dissection has significant staging, prognosis and follow-up implications.	3
Low-quality data suggest that tumour thrombus excision in non-metastatic disease may be beneficial.	3

Recommendations	**Strength rating**
During nephrectomy, remove clinically enlarged lymph nodes for staging, prognosis and follow-up implications.	Weak
Remove the renal tumour and thrombus in case of venous involvement in non-metastatic disease.	Strong
In case of metastatic disease, discuss surgery within the context of a multi-disciplinary team.	Weak

*7.2.5 **Neoadjuvant and adjuvant therapy***

Neoadjuvant therapy is currently under investigation and available in clinical trials.

There is currently no evidence from a recent systematic review (including ten retrospective studies and two RCTs) that adjuvant radiation therapy increases survival [418].

The impact on OS of adjuvant tumour vaccination in selected patients undergoing nephrectomy for T3 renal carcinomas remains unconfirmed [419-423] (LE: 1b). A similar observation was made in an adjuvant trial of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER Study) [424].

At present, there is no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. Thus far, several RCTs comparing VEGFR-TKI vs. placebo have been published [425-432]. One of the largest adjuvant trials compared sunitinib vs. sorafenib vs. placebo (ASSURE). Its interim results published in 2015 demonstrated no significant differences in DFS or OS between the experimental arms and placebo [391]. The study published its updated analysis on a subset of high-risk patients in 2018, which demonstrated five-year DFS rates of 47.7%, 49.9%, and 50.0%, respectively for sunitinib, sorafenib, and placebo and five-year OS of 75.2%, 80.2%, and 76.5%, respectively, without significant difference. The results indicated that adjuvant therapy with sunitinib or sorafenib have no survival effect [425, 426].

The PROTECT study included 1,135 patients treated with pazopanib (n = 571) vs. placebo (n = 564) in a 1:1 randomisation [427]. The primary endpoint was amended after 403 patients received a starting dose of pazopanib 800 mg vs. placebo, to DFS with pazopanib 600 mg. The primary analysis results of DFS in the ITT pazopanib 600 mg arm were not significant (HR: 0.86, 95% CI: 0.7–1.06, p = 0.16). Disease-free survival in the ITT pazopanib 800 mg population was improved (HR: 0.69, 95% CI: 0.51–0.94, p = 0.02). No benefit in OS was seen in the ITT pazopanib 600 mg population (HR: 0.79 [0.57–1.09, p = 0.16]). A subset analysis of these studies suggests that full-dose therapy is associated with improved DFS. Furthermore, no strong association of DFS with OS has been established [428].

The ATLAS study, a randomised, double-blind phase III trial including patients receiving (1:1) oral twice-daily axitinib 5 mg or placebo for ≤ 3 years, for a minimum of one year unless patients experienced a recurrence, had a second primary malignancy, significant toxicity, or withdrew consent. The primary endpoint was DFS. A total of 724 patients (363 vs. 361, for axitinib vs. placebo) were randomised. The trial was stopped due to futility at a pre-planned interim analysis at 203 DFS events. There was no significant difference in DFS per independent review committee (IRC) (HR: 0.870, 95% CI: 0.660–1.147, p = 0.3211). Overall survival data were not mature. Similar AEs (99% vs. 92%) and serious AEs (19% vs. 14%), but more grade 3/4 AEs (61% vs. 30%) were reported for axitinib vs. placebo [431].

In contrast, the S-TRAC study included 615 patients randomised to either sunitinib or placebo [433]. The results showed a benefit of sunitinib over placebo for DFS (HR: 0.76, 95% CI: 0.59–0.98, p = 0.03). Grade 3/4 toxicity in the study was 60.5% for patients receiving sunitinib, which translated into significant differences in QoL for loss of appetite and diarrhoea [432]. The study published its updated results in 2018; the results for DFS had not changed significantly (HR: 0.74, 95% CI: 0.55–0.99, p = 0.04) and median OS was not reached in either arm (HR: 0.92, 95% CI: 0.66–1.28, p = 0.6) [432].

The last trial being reported is the SORCE RCT which investigated one and three years of adjuvant sorafenib and which also included patients with non-clear cell subtypes [434]. In SORCE no differences in DFS or OS for patients with high risk of recurrence, or patients with ccRCC only was found. Median DFS was not reached for three years of sorafenib or for placebo (HR: 1.01, 95% CI: 0.83–1.23; p = 0.95), and OS was different (HR: 1.06, 95% CI: 0.82–1.38; p = 0.638). More than half of participants stopped treatment by twelve months. Adverse event rates grade ≥ 3 were 58.6% and 63.9% receiving one year or three years of sorafenib [434].

To date, the results of one RCT on the role of adjuvant everolimus (EVEREST) in patients with RCC is still unpublished.

A recent meta-analysis of phase III randomised clinical trials on adjuvant TKIs in ccRCC was published [435]. In the overall population, the pooled HR of OS and DFS was 0.89 (95% CI: 0.76–1.04) and 0.84 (95% CI: 0.76–0.93), respectively. In the low- and high-risk populations, the pooled DFS HR was 0.98 (95% CI: 0.82–1.17) and 0.85 (95% CI: 0.75–0.97), respectively. Adjuvant use of TKIs does not appear to provide a statistically significant OS benefit. However, a benefit in DFS has been observed in overall and high-risk populations, suggesting that better selection of patients might be important for the evaluation of adjuvant therapies in RCC, although these results must be balanced against significant toxicity.

In summary, there is currently a lack of proven benefits of adjuvant therapy with VEGFR-TKIs for patients with high-risk RCC after nephrectomy. The European Medicines Agency (EMA) has not approved sunitinib for adjuvant treatment of high-risk RCC in adult patients after nephrectomy.

Immune checkpoint inhibitors, designed to restore and enhance immune activity against cancer cells, have shown impressive efficacy in the metastatic setting. Several trials have tested these agents in metastatic RCC, leading to a still-ongoing revolution in the treatment pathway. The inclusion of these drugs in clinical practice has led to a third generation of adjuvant studies on ICIs. These include the programmed death receptor-1

inhibitors nivolumab (PROSPER; NCT03055013), pembrolizumab (KEYNOTE-564; NCT03142334), as well as the programmed death ligand-1 inhibitors atezolizumab (IMmotion010; NCT03024996) and durvalumab (RAMPART [Renal Adjuvant MultiPle Arm Randomised Trial]; NCT03288532). Recruitment for most of these studies is still ongoing and except for KEYNOTE-564, results are awaited as of 2022-2023.

The Keynote-564 trial is the first trial to report positive primary endpoint data on DFS [436]. Keynote-564 evaluated pembrolizumab (17 cycles of 3-weekly therapy) vs. placebo as adjuvant therapy for 994 patients with intermediate (pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0, M0) or high risk (pT4, any grade, N0 M0; or pT any stage, and grade, or N+, M0), or M1 [no evidence of disease (NED) after primary tumour plus soft tissue metastases completely resected ≤ one year from nephrectomy] disease. The median follow-up, defined as time from randomisation to data cut-off, was 24.1 months. The primary endpoint of DFS per investigator assessment was significantly improved in the pembrolizumab group vs. placebo (HR: 0.68, 95% CI: 0.53-0.87, p = 0.001). The estimated 24-month DFS rate was 77% vs. 68% for pembrolizumab and placebo, respectively. Benefit occurred across broad subgroups of patients including those with M1/NED disease post-surgery (n = 58 [6%]). Investigator assessed DFS was considered preferable to DFS by central review due to its clinical applicability. Overall survival showed a non-statistically significant trend towards a benefit in the pembrolizumab arm (HR: 0.54, 95% CI: 0.30-0.96, p = 0.0164). Follow-up was short and few OS events occurred (two-year OS rate of 97% [pembrolizumab] vs. 94% [placebo]). Grade 3-5 all-cause AEs occurred in 32% vs. 18% of patients for pembrolizumab and placebo, respectively. Quality of life assessment by FKSI-DRS and QLQ30 did not show a statistically significant or clinically meaningful deterioration in health-related QoL or symptom scores for either adjuvant pembrolizumab or placebo.

After GRADE assessment the Panel members reached consensus and issued a weak recommendation for adjuvant pembrolizumab for patients with high-risk (defined as per study) operable ccRCC until final OS data are available [437]. Although the guidelines previously did not recommend sunitinib despite positive DFS data in the absence of OS benefit [432, 433, 438], the Panel decided for adjuvant pembrolizumab for the following reasons:

- Immune checkpoint inhibitor therapy has a different mode of action than VEGFR-TKI resulting in complete responses in up to 16% of patients in PD-1 unselected populations in metastatic disease [439]. Despite immature OS data with the early OS signal potentially driven by the M1 population the Panel cannot exclude that a survival benefit will emerge. This was not the case in the adjuvant sunitinib trial (STRAC) [432, 436].
- Pembrolizumab is better tolerated than sunitinib and does not lead to a decline of QoL compared to placebo as did sunitinib [436, 440].
- A number of adjuvant VEGFR trials failed to show a DFS advantage for sunitinib or other VEFGR inhibitors resulting in a negative meta-analysis [441].

The Panel considered the following cautionary points in their decision leading to a weak recommendation:

- A high proportion of patients, cured by surgery, are receiving unnecessary, and potentially harmful treatment.
- The tolerability profile is acceptable but grade 3-5 AEs were higher with 14.7% in the pembrolizumab arm as in the placebo arm (occurring in approximately one-third of patients, all cause). Approximately 18% of patients required treatment discontinuation early for AEs which gives a broad indicator of tolerability. Endocrine AEs may require life-long therapy.
- Other ICI trials have not yet reported and are not available for meta-analysis.
- Biomarker analysis to predict outcome and AEs are not available.
- Final OS data are not yet available.

Table 7.1: Updated EAU RCC guideline recommendation for the adjuvant treatment of high-risk ccRCC [437]

Phase III trial of PD-1 immune checkpoint inhibitors in adjuvant RCC						
Study	**N**	**Experimental arm**	**Primary endpoint**	**Risk groups**	**DFS (mo) Median (95% CI) HR**	**OS (mo) Median (95% CI) HR**
Keynote-564 NCT03142334 Median follow-up of 24.1 mo. [436]	994	PEMBRO 200 mg IV Q3W (17 cycles) vs. placebo	DFS in the ITT by IR	**Intermediate-high:** pT2 grade 4 or sarcomatoid; pT3 any grade **High:** pT4 any grade, pN1 **M1 NED:** cM0 after resection of oligometastatic disease < 12 mo.	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE) HR: 0.68 (95% CI: 0.53-0.87) p < 0.002 DFS at 24 mo.: PEMBRO: 77.3% PLACEBO: 68.1%	(ITT) PEMBRO: NR (NE) PLACEBO: NR (NE) HR: 0.54 (95% CI: 0.30-0.96) not significant alive at 24 mo.: PEMBRO: 96.6% PLACEBO: 93.5%

CI = confidence interval; HR = hazard ratio; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; NE = non-estimable; NED = no evidence of disease; NR = not reached; OS = overall survival; PD-1 = programmed death-receptor 1; PEMBRO = pembrolizumab; PFS = profession-free survival; Q3W = every 3 weeks.

7.2.5.1 Summary of evidence and recommendations for neoadjuvant and adjuvant therapy

Summary of evidence	LE
Adjuvant tyrosine kinase inhibitor therapy does not improve OS after nephrectomy.	1b
In one single RCT, in selected high-risk patients, adjuvant sunitinib improved DFS but not OS.	1b
Adjuvant sorafenib, pazopanib, everolimus, girentuximab or axitinib does not improve DFS or OS after nephrectomy.	1b
Adjuvant pembrolizumab after nephrectomy in patients with high-risk RCC improves PFS.	1b
In one RCT, in selected intermediate-high or high-risk patients or M1 NED, adjuvant pembrolizumab improved DFS.	1b
Adjuvant RCTs are ongoing to evaluate the benefit of adjuvant immunotherapy after nephrectomy in high-risk patients.	1b

Recommendations	Strength rating
Do not offer adjuvant therapy with sorafenib, pazopanib, everolimus, girentuximab or axitinib.	Strong
Do not offer adjuvant sunitinib following surgically resected high-risk clear-cell renal cell carcinoma (ccRCC).	Weak
Offer adjuvant pembrolizumab to patients with ccRCC following surgery with curative intent with a risk of recurrence as defined in the trial.*	Weak

** pT2 G4 or pT3 any G; pT4 any G; pN+ Any G.*

7.3 Advanced/metastatic RCC

*7.3.1 **Local therapy of advanced/metastatic RCC***

7.3.1.1 Cytoreductive nephrectomy

Tumour resection is potentially curative only if all tumour deposits are excised. This includes patients with the primary tumour in place and single- or oligometastatic resectable disease. For most patients with metastatic disease, cytoreductive nephrectomy (CN) is palliative and systemic treatments are necessary. In a combined analysis of two RCTs comparing CN+ IFN-based immunotherapy vs. IFN-based immunotherapy only, increased long-term survival was found in patients treated with CN [442].

However, IFN-based immunotherapy is no longer relevant in contemporary clinical practice. In order to investigate the role and sequence of CN in the era of targeted therapy, a structured literature assessment was performed to identify relevant RCTs and systematic reviews published between July 1st - June 30th 2019. Two RCTs [400, 443] and a narrative systematic review were identified [444]. The narrative systematic review

included both RCTs and ten non-randomised studies. CARMENA, a phase III non-inferiority RCT investigating immediate CN followed by sunitinib vs. sunitinib alone, showed that sunitinib alone was not inferior to CN followed by sunitinib with regard to OS [445]. The trial included 450 patients with metastatic ccRCC of intermediate- and MSKCC poor-risk of whom 226 were randomised to immediate CN followed by sunitinib and 224 to sunitinib alone. Patients in both arms had a median of two metastatic sites. Patients in both arms had a tumour burden of a median/mean of 140 mL of measurable disease by Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, of which 80 mL accounted for the primary tumour. The study did not reach the full accrual of 576 patients and the Independent Data Monitoring Commission (IDMC) advised the trial steering committee to close the study. In an ITT analysis after a median follow-up of 50.9 months, median OS with CN was 13.9 months vs. 18.4 months with sunitinib alone (HR: 0.89, 95% CI: 0.71–1.10). This was found in both risk groups. For MSKCC intermediate-risk patients (n = 256) median OS was 19.0 months with CN and 23.4 months with sunitinib alone (HR: 0.92, 95% CI: 0.60–1.24) and for MSKCC poor risk (n = 193) 10.2 months and 13.3 months, respectively (HR: 0.86, 95% CI: 0.62–1.17). Non-inferiority was also found in two per-protocol analyses accounting for patients in the CN arm who either did not undergo surgery (n = 16) or did not receive sunitinib (n = 40), and patients in the sunitinib-only arm who did not receive the study drug (n = 11). Median PFS in the ITT population was 7.2 months with CN and 8.3 months with sunitinib alone (HR: 0.82, 95% CI: 0.67–1.00). The clinical benefit rate, defined as disease control beyond twelve weeks was 36.6% with CN and 47.9% with sunitinib alone (p = 0.022). Of note, 38 patients in the sunitinib-only arm required secondary CN due to acute symptoms or for complete or near-complete response. The median time from randomisation to secondary CN was 11.1 months.

The randomised EORTC SURTIME study revealed that the sequence of CN and sunitinib did not affect PFS (HR: 0.88, 95% CI: 0.59–1.37, p = 0.569). The trial accrued poorly and therefore results are mainly exploratory. However, in secondary endpoint analysis a strong OS benefit was observed in favour of the deferred CN approach in the ITT population with a median OS of 32.4 (range 14.5–65.3) months in the deferred CN arm vs. 15.0 (9.3–29.5) months in the immediate CN arm (HR: 0.57, 95% CI: 0.34–0.95, p = 0.032). The deferred CN approach appears to select out patients with inherent resistance to systemic therapy [446]. This confirms previous findings from single-arm phase II studies [444, 447]. Moreover, deferred CN and surgery appear safe after sunitinib which supports the findings, with some caution, of the only available RCT. In patients with poor PS or IMDC poor risk, small primaries and high metastatic volume and/or a sarcomatoid tumour, CN is not recommended [448]. These data are confirmed by CARMENA [445] and upfront pre-surgical VEGFR-targeted therapy followed by CN seems to be beneficial [449].

Meanwhile first-line therapy recommendations for patients with their primary tumour in place have changed to ICI combination therapy (see Section 7.4.2.4) with sunitinib and other VEGFR-TKI monotherapies reserved for those who cannot tolerate ICI combination or have no access to these drugs. High-level evidence regarding CN is not available for ICI combinations but up to 30% of patients with primary metastatic disease, treated with their tumour in place, were included in the pivotal ICI combination trials (Table 7.2). The subgroup HRs, where available, suggest better outcomes for the ICI combination compared to sunitinib monotherapy. In mRCC patients without a need for immediate drug treatment, a recent systematic review evaluating effects of CN demonstrated an OS advantage of CN [444]. These data were supported by a nation-wide registry study showing that patients selected for primary CN had a significant OS advantage across all age groups [450].

Table 7.2: Key trials on immune checkpoint inhibitor combinations for primary metastatic disease

Trial	Drug combination	Number and % of patients treated with primary tumour in place	Number of patients treated with the primary tumour in place (ICI combination vs. sunitinib)		Subgroup analyses (HR with 95% CIs)	
			ICI combination	sunitinib	PFS	OS
CheckMate 214 [451]	ipilimumab + nivolumab	187/847 (22%)	84	103	NA	0.63 (0.42–0.94)
CheckMate 9ER [452]	cabozantinib + nivolumab	196/651 (30.1%)	101	95	0.63 (0.43–0.92)	0.79 (0.48–1.29)
Javelin 101 [453]	axitinib + avelumab	179/886 (20.2%)	90	89	0.75 (0.48–1.65)	NA

KEYNOTE-426 [454]	axitinib + pembrolizumab	143/861 (16.6%)	73	70	0.68 (0.45–1.03)	0.57 (0.36–0.89)
CLEAR [455]	lenvatinib + pembrolizumab	179/714 (25.1%)	97	82	0.38 (0.31-0.48)	0.52 (0.31-0.86)

CI = confidence interval; HR = hazard ratio; ICI = immune checkpoint inhibitor; NA = not available; PFS = profession-free survival; OS = overall survival.

The results of CARMENA and SURTIME demonstrated that patients who require systemic therapy benefit from immediate drug treatment. While randomised trials to investigate deferred vs. no cytoreductive nephrectomy with ICI and ICI combinations are ongoing, the exploratory results from the ICI combination trials demonstrate that the respective IO+IO or TKI+IO combinations have a superior effect on the primary tumour and metastatic sites when compared to sunitinib alone (Table 7.2). In accordance with the CARMENA and SURTIME data this suggests that mRCC patients and IMDC intermediate- and poor-risk groups with their primary tumour in place should be treated with upfront IO-based combinations. In patients with a clinical response to IO-based combinations, a subsequent CN may be considered.

7.3.1.1.1 Embolisation of the primary tumour

In patients unfit for surgery or with non-resectable disease, embolisation can control symptoms including visible haematuria or flank pain [291, 292, 401] (see recommendations Section 7.1.2.2.4).

7.3.1.1.2 Summary of evidence and recommendations for local therapy of advanced/metastatic RCC

Summary of evidence	**LE**
Deferred CN with pre-surgical sunitinib in intermediate-risk patients with cc-mRCC shows a survival benefit in secondary endpoint analyses and selects out patients with inherent resistance to systemic therapy.	2b
Sunitinib alone is non-inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk who require systemic therapy with VEGFR-TKI.	1a
Cytoreductive nephrectomy in patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.	3
Patients with MSKCC or IMDC poor risk (≥ 4 risk factors) do not benefit from local therapy.	1a
Patients with their primary tumour in place treated with IO-based combination therapy have better PFS and OS in exploratory subgroup analyses compared to treatment with sunitinib.	2b

Recommendations	**Strength rating**
Do not perform cytoreductive nephrectomy (CN) in MSKCC poor-risk patients.	Strong
Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy.	Weak
Discuss delayed CN with patients who derive clinical benefit from systemic therapy.	Weak
Perform immediate CN in patients with a good performance status who do not require systemic therapy.	Weak
Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved.	Weak

*7.3.2 **Local therapy of metastases in metastatic RCC***

A systematic review of the local treatment of metastases from RCC in any organ was undertaken [456]. Interventions included metastasectomy, various radiotherapy modalities, and no local treatment. The outcomes assessed were OS, CSS and PFS, local symptom control and AEs. A risk-of-bias assessment was conducted [457]. Of the 2,235 studies identified only sixteen non-randomised comparative studies were included.

Eight studies reported on local therapies of RCC-metastases in various organs [458-465]. This included metastases to any single organ or multiple organs. Three studies reported on local therapies of RCC metastases in bone, including the spine [466-468], two in the brain [469, 470] and one each in the liver [471] lung [472] and pancreas [473]. Three studies were published as abstracts only [461, 463, 472]. Data were too

heterogeneous to meta-analyse. There was considerable variation in the type and distribution of systemic therapies (cytokines and VEGF-inhibitors) and in reporting the results.

7.3.2.1 Complete versus no/incomplete metastasectomy

A systematic review, including only eight studies, compared complete vs. no and/or incomplete metastasectomy of RCC metastases in various organs [458-465]. In one study complete resection was achieved in only 45% of the metastasectomy cohort, which was compared with no metastasectomy [465]. Non-surgical modalities were not applied. Six studies [459-461, 463-465] reported a significantly longer median OS or CSS following complete metastasectomy (the median value for OS or CSS was 40.75 months, range 23–122 months) compared with incomplete and/or no metastasectomy (the median value for OS or CSS was 14.8 months, range 8.4–55.5 months). Of the two remaining studies, one [458] showed no significant difference in CSS between complete and no metastasectomy, and one [462] reported a longer median OS for metastasectomy albeit no p-value was provided.

Three studies reported on treatment of RCC metastases in the lung [472], liver [471], and pancreas [473], respectively. The lung study reported a significantly higher median OS for metastasectomy vs. medical therapy only for both targeted therapy and immunotherapy. Similarly, the liver and pancreas study reported a significantly higher median OS and five-year OS for metastasectomy vs. no metastasectomy.

7.3.2.2 Local therapies for RCC bone metastases

Of the three studies identified, one compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with RCC bone metastases [468]. Single-dose IGRT (≥ 24 Gy) had a significantly better three-year actuarial local PFS rate, also shown by Cox regression analysis. Another study compared metastasectomy/curettage and local stabilisation with no surgery of solitary RCC bone metastases in various locations [466]. A significantly higher five-year CSS rate was observed in the intervention group. After adjusting for prior nephrectomy, gender and age, multi-variable analysis still favoured metastasectomy/curettage and stabilisation. A third study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy in patients with RCC bone metastases to the spine [467]. Pain, ORR, time-to-pain relief and duration of pain relief were similar.

7.3.2.3 Local therapies for RCC brain metastases

Two studies on RCC brain metastases were included. A three-armed study compared stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) vs. SRS and WBRT [469]. Each group was further subdivided into recursive partitioning analysis (RPA) classes I to III (I favourable, II moderate and III poor patient status). Two-year OS and intra-cerebral control were equivalent in patients treated with SRS alone and SRS plus WBRT.

Both treatments were superior to WBRT alone in the general study population and in the RPA subgroup analyses. A comparison of SRS vs. SRS and WBRT in a subgroup analysis of RPA class I showed significantly better two-year OS and intra-cerebral control for SRS plus WBRT based on only three participants. The other study compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy alone [470]. Several patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. One-, two- and three-year survival rates were higher but not significantly so for FSRT as for metastasectomy and conventional radiotherapy, or conventional radiotherapy alone. Fractionated stereotactic radiotherapy did not result in a significantly better two-year local control rate compared with metastasectomy plus conventional radiotherapy.

7.3.2.4 Embolisation of metastases

Embolisation prior to resection of hypervascular bone or spinal metastases can reduce intra-operative blood loss [166]. In selected patients with painful bone or paravertebral metastases, embolisation can relieve symptoms [167] (see recommendation Section 7.1.2.2.4).

7.3.2.5 Adjuvant treatment in cM0 patients after metastasectomy

Patients after metastasectomy and no evidence of disease (cM0) have a high risk of relapse. Recent attempts to reduce RFS by offering adjuvant TKI treatment after metastasectomy did not demonstrate an improvement in RFS. In a recent phase II trial 129 patients were randomised to either pazopanib 800 mg daily vs. placebo for 52 weeks. The primary study endpoint of a 42% DFS improvement from 25% to 45% at three years was not met. Hazard ratio for DFS in pazopanib vs. placebo-treated patients was 0.85 (0.55–1.31), p = 0.47 [168]. A second phase II trial randomised 69 ccRCC patients after metastasectomy and no evidence of disease to either sorafenib (400 mg twice daily) or observation. The study was terminated early due to slow accrual and the availability of new agents and multimodal treatment options, including surgery or a locoregional approach. The primary endpoint of RFS was not reached with a RFS of 21 months in the sorafenib arms vs. 37 months in the observation arm (p = 0.404) [169].

KEYNOTE-564 included a small percentage of patients who were treated by nephrectomy and complete metastasectomy within one year after primary diagnosis (6% in the experimental arm and 6% in the placebo arm) [436]. A metachronous interval of < 1 year for recurrences following surgery with curative intent is a poor prognostic factor by IMDC classification [249, 474]. Systemic therapy based on immune combinations has stronger levels of evidence than surgery in this intermediate/advanced disease setting [475]. Also, TKI-driven adjuvant trials after metastasectomy have shown no DFS or OS benefit [168, 169].

Results for single-agent pembrolizumab post-surgery for metastatic disease are therefore difficult to interpret due to the small subgroup. Nevertheless, the DFS HR of 0.29 (95% CI: 0.12-0.69) in favour of resection of M1 to NED plus pembrolizumab shows that patients with subclinical, but progressive disease who were subjected to metastasectomy had a benefit of adjuvant systemic therapy with pembrolizumab. Based on the current data it cannot be concluded that for patients with oligo-progressive disease, metastasectomy within the first year of initial diagnosis of the primary and subsequent adjuvant pembrolizumab is superior to a period of observation and dual IO based combination first-line therapy upon progression. Data from the TKI era suggest that patients with oligometastatic disease recurrence can be observed for up to a median of sixteen months before systemic therapy is required and that this practice is common in real-world settings (30%) [476, 477].

In addition, it is possible that metastatectomy may lead to poorer outcomes compared to systemic therapy approaches as a relapse within the first twelve months and presentation with synchronous (oligo-) metastatic disease is attributed to the IMDC intermediate risk-group. The Panel therefore does not encourage metastasectomy and adjuvant pembrolizumab in this advanced population with recurrent disease within one year after primary surgery. A careful reassessment of disease status to rule out rapid progressive disease should be performed. Data from other adjuvant ICI studies including M1 NED subgroups may clarify this issue further (IMmotion010, NCT03024996).

7.3.2.6 Summary of evidence and recommendations for local therapy of metastases in metastatic RCC

Summary of evidence	**LE**
All studies included in the Panel systematic review were retrospective non-randomised comparative studies, resulting in a high risk of bias associated with non-randomisation, attrition, and selective reporting.	3
Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of OS, CSS and delay of systemic therapy.	3
A single-arm prospective and retrospective study support that oligometastases can be observed for up to 16 months before systemic therapy is required due to progression.	3
Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g., pain).	3
Tyrosine kinase inhibitors treatment after metastasectomy in patients with no evidence of disease did not improve RFS when compared to placebo or observation.	1b

Recommendations	**Strength rating**
To control local symptoms, offer ablative therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and in whom complete resection is achievable.	Weak
Offer stereotactic radiotherapy for clinically relevant bone- or brain metastases for local control and symptom relief.	Weak
Do not offer tyrosine kinase inhibitor treatment to mRCC patients after metastasectomy and no evidence of disease.	Strong
Perform a confirmatory axial scan of disease status prior to metastasectomy to rule out rapid progressive metastatic disease which requires systemic treatment.	Weak
Before initiating systemic therapy for oligometastases that cannot be resected, discuss with your patient a period of observation until progression is confirmed.	Weak

7.4 Systemic therapy for advanced/metastatic RCC

*7.4.1 **Chemotherapy***

Chemotherapy has proven to be generally ineffective in the treatment of RCC but can be offered in rare patients, with the exception of collecting duct and medullary carcinoma [170].

7.4.1.1 Recommendation for systemic therapy in advanced/metastatic RCC

Recommendation	Strength rating
Do not offer chemotherapy to patients with metastatic renal cell carcinoma.	Strong

*7.4.2 **Targeted therapies***

In sporadic ccRCC, hypoxia-inducible factor (HIF) accumulation due to VHL-inactivation results in overexpression of VEGF and platelet-derived growth factor (PDGF), which promote neo-angiogenesis [478-480]. This process substantially contributes to the development and progression of RCC. Several targeting drugs for the treatment of mRCC are approved in both the USA and Europe.

Most published trials have selected for clear-cell carcinoma subtypes, thus no robust evidence-based recommendations can be given for non-ccRCC subtypes.

In major trials leading to registration of the approved targeted agents, patients were stratified according to the IMDC risk model (Table 7.3) [251].

Table 7.3: Median OS and percentage of patients surviving two years treated in the era of targeted therapy per IMDC risk group*#

IMDC Model	Patients#		Median OS* (months)	2-yr OS (95% CI)#
	n	%		
Favourable	157	18	43.2	75% (65–82%)
Intermediate	440	52	22.5	53% (46–59%)
Poor	252	30	7.8	7% (2–16%)

** Based on [251]; # based on [474].*
CI = confidence interval; IMDC = Metastatic Renal Cancer Database Consortium; n = number of patients; OS = overall survival; yr = year.

7.4.2.1 Tyrosine kinase inhibitors

7.4.2.1.1 Sorafenib

Sorafenib is an oral multi-kinase inhibitor. A trial compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unfit for immunotherapy. Sorafenib improved PFS (HR: 0.44, 95% CI: 0.35–0.55, $p < 0.01$) [481]. Overall survival improved in patients initially assigned to placebo who were censored at crossover [482].

In patients with previously untreated mRCC sorafenib was not superior to IFN-α (phase II study). A number of studies have used sorafenib as the control arm in sunitinib-refractory disease vs. axitinib, dovitinib or temsirolimus. None showed superior survival for the study drug compared to sorafenib.

7.4.2.1.2 Sunitinib

Sunitinib is an oral TKI inhibitor and has anti-tumour and anti-angiogenic activity. First-line monotherapy with sunitinib demonstrated significantly longer PFS compared with IFN-α. Overall survival was greater in patients treated with sunitinib (26.4 months) vs. IFN-α (21.8 months) despite crossover [483].

In the EFFECT trial, sunitinib 50 mg/day (four weeks on/two weeks off) was compared with continuous uninterrupted sunitinib 37.5 mg/day in patients with cc-mRCC [484]. No significant differences in OS were seen (23.1 vs. 23.5 months, $p = 0.615$). Toxicity was comparable in both arms. Because of the non-significant, but numerically longer time to progression with the standard 50 mg dosage, the authors recommended using this regimen. Alternate scheduling of sunitinib (two weeks on/one week off) is being used to manage toxicity, but robust data to support its use is lacking [485, 486].

7.4.2.1.3 Pazopanib

Pazopanib is an oral angiogenesis inhibitor. In a trial of pazopanib vs. placebo in treatment-naïve mRCC patients and cytokine-treated patients, a significant improvement in PFS and tumour response was observed [487].

A non-inferiority trial comparing pazopanib with sunitinib (COMPARZ) established pazopanib as

an alternative to sunitinib. It showed that pazopanib was not associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles, and QoL was better with pazopanib [488]. In another patient-preference study (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, $p < 0.05$) due to symptomatic toxicity [489]. Both studies were limited in that intermittent therapy (sunitinib) was compared with continuous therapy (pazopanib).

7.4.2.1.4 Axitinib

Axitinib is an oral selective second-generation inhibitor of VEGFR-1, -2, and -3. Axitinib was first evaluated as second-line treatment. In the AXIS trial, axitinib was compared to sorafenib in patients who had previously failed cytokine treatment or targeted agents (mainly sunitinib) [490].

The overall median PFS was greater for axitinib than sorafenib. Axitinib was associated with a greater PFS than sorafenib (4.8 vs. 3.4 months) after progression on sunitinib. Axitinib showed grade 3 diarrhoea in 11%, hypertension in 16%, and fatigue in 11% of patients. Final analysis of OS showed no significant differences between axitinib or sorafenib [491, 492]. In a randomised phase III trial of axitinib vs. sorafenib in first-line treatment-naïve cc-mRCC, a significant difference in median PFS between the treatment groups was not demonstrated, although the study was underpowered, raising the possibility of a type II error [493]. As a result of this study, axitinib is not approved for first-line therapy.

7.4.2.1.5 Cabozantinib

Cabozantinib is an oral inhibitor of tyrosine kinase, including MET, VEGF and AXL. Cabozantinib was investigated in a phase I study in patients resistant to VEGFR and mTOR inhibitors demonstrating objective responses and disease control [221]. Based on these results an RCT investigated cabozantinib vs. everolimus in patients with ccRCC failing one or more VEGF-targeted therapies (METEOR) [494, 495]. Cabozantinib delayed PFS compared to everolimus in VEGF-targeted therapy refractory disease (HR: 0.58, 95% CI: 0.45–0.75) [494] (LE: 1b). The median OS was 21.4 months (95% CI: 18.7 to not estimable) with cabozantinib and 16.5 months (95% CI: 14.7–18.8) with everolimus in VEGF-resistant RCC. The HR for death was 0.66 (95% CI: 0.53–0.83, $p = 0.0003$) [495]. Grade 3 or 4 AEs were reported in 74% with cabozantinib and 65% with everolimus. Adverse events were managed with dose reductions; doses were reduced in 60% of the patients who received cabozantinib.

The Alliance A031203 CABOSUN randomised phase II trial comparing cabozatinib and sunitinib in first-line in 157 intermediate- and poor-risk patients favoured cabozantinib for RR and PFS, but not OS [496, 497]. Cabozantinib significantly increased median PFS (8.2 vs. 5.6 months, adjusted HR: 0.66, 95% CI: 0.46 to 0.95; one-sided $p = 0.012$). Objective response rate was 46% (95% CI: 34–57) for cabozantinib vs. 18% (95% CI: 10–28) for sunitinib. All-causality grade 3 or 4 AEs were similar for cabozantinib and sunitinib. No difference in OS was seen. Due to limitations of the statistical analyses within this trial, the evidence is inferior over existing choices.

7.4.2.1.6 Lenvatinib

Lenvatinib is an oral multi-target TKI of VEGFR1, VEGFR2, and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3, and FGFR4), platelet growth factor receptor (PDGFR-α), re-arranged during transfection (RET) and receptor for stem cell factor (KIT). It has recently been investigated in a randomised phase II study in combination with everolimus vs. lenvatinib or everolimus alone (see Section 7.4.4.1.1 for discussion of results) [498].

7.4.2.1.7 Tivozanib

Tivozanib is a potent and selective TKI of VEGFR1, VEGFR2, and VEGFR3 and was compared in two phase III trials with sorafenib in patients with mRCC [499, 500]. Tivozanib was approved by the EMA in front-line mRCC. While it was associated with a PFS advantage in both studies, no OS advantage was seen. In view of the choice of sorafenib as the control arm in the front-line trial, the Panel considers there is too much uncertainty, and too many attractive alternatives, to support its use in this front-line setting.

7.4.2.2 Monoclonal VEGF antibody

Bevacizumab is a humanised monoclonal antibody. The double-blind AVOREN study compared bevacizumab plus IFN-α with IFN-α monotherapy in mRCC. Overall response was higher in the bevacizumab plus IFN-α group. Median PFS increased from 5.4 months with IFN-α to 10.2 months with bevacizumab plus IFN-α. No benefit was seen in MSKCC poor-risk patients. Median OS in this trial, which allowed crossover after progression, was not greater in the bevacizumab/IFN-α group (23.3 vs. 21.3 months) [501].

An open-label trial (CALGB 90206) of bevacizumab plus IFN-α vs. IFN-α showed a higher median PFS for the combination group [502, 503]. Objective response rate was also higher in the combination group. Overall toxicity was greater for bevacizumab plus IFN-α, with significantly more grade 3 hypertension, anorexia,

fatigue, and proteinuria. Bevacizumab, alone, or in combinations, is not widely recommended or used in mRCC due to more attractive alternatives.

7.4.2.3 mTOR inhibitors

7.4.2.3.1 Temsirolimus

Temsirolimus is a specific inhibitor of mTOR [504]. Its use has been superseded as front-line treatment option.

7.4.2.3.2 Everolimus

Everolimus is an oral mTOR inhibitor, which is established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus plus best supportive care (BSC) vs. placebo plus BSC in patients with previously failed anti-VEGFR treatment (or previously intolerant of VEGF-targeted therapy) [505]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [505].

The Panel consider, even in the absence of conclusive data, that everolimus may present a therapeutic option in patients who were intolerant to, or previously failed, immune- and VEGFR-targeted therapies (LE: 4). Recent phase II data suggest adding lenvatinib is attractive.

7.4.2.4 Summary of evidence and recommendations for targeted therapy in metastatic clear-cell RCC

Summary of evidence	**LE**
Single-agent VEGF-targeted therapy has been superseded by immune checkpoint-based combination therapy.	1b
Pazopanib is non-inferior to sunitinib in front-line mRCC.	1b
Cabozantinib in intermediate- and poor-risk treatment-naïve ccRCC leads to better response rates and PFS but not OS when compared to sunitinib.	2b
Tivozanib has been EMA approved, but the evidence is still considered inferior over existing choices in the front-line setting.	3
Single-agent VEGF-targeted therapies are preferentially recommended after front-line PD-L1-based combinations. Re-challenge with treatments already used should be avoided.	3
Single-agent cabozantinib or nivolumab are superior to everolimus after one or more lines of VEGF-targeted therapy.	1b
Everolimus prolongs PFS after VEGF-targeted therapy when compared to placebo. This is no longer widely recommended before third-line therapy.	1b
Lenvatinib in combination with everolimus improved PFS over everolimus alone in VEGF-refractory disease. Its role after ICIs is uncertain. There is a lack of robust data on this combination making its recommendation challenging.	2a

Recommendations	**Strength rating**
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naïve vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
Sequencing the agent not used as second-line therapy (nivolumab or cabozantinib) for third-line therapy is recommended.	Weak
Offer VEGF-tyrosine kinase inhibitors as second-line therapy to patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab or cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Offer cabozantinib after VEGF-targeted therapy in cc-mRCC.	Strong
Sequence systemic therapy in treating mRCC.	Strong
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

7.4.3 ***Immunotherapy***

7.4.3.1 Immune checkpoint inhibitors

7.4.3.1.1 Immuno-oncology monotherapy

Immune checkpoint inhibitor with monoclonal antibodies targets and blocks the inhibitory T-cell receptor PD-1 or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)-signalling to restore tumour-specific T-cell immunity [506]. Immune checkpoint inhibitor monotherapy has been investigated as second- and third-line therapy. A phase III trial of nivolumab vs. everolimus after one or two lines of VEGF-targeted therapy for mRCC with a

clear cell component (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 AEs with nivolumab than with everolimus [507]. Nivolumab has superior OS to everolimus (HR: 0.73, 95% CI: 0.57–0.93, p < 0.002) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus with a five-year OS probability of 26% vs. 18% [508] (LE: 1b). Patients who had failed multiple lines of VEGF-targeted therapy were included in this trial making the results broadly applicable. The trial included 15% MSKCC poor-risk patients. There was no PFS advantage with nivolumab despite the OS advantage. Progression-free survival does not appear to be a reliable surrogate of outcome for PD-1 therapy in RCC. Currently PD-L1 biomarkers are not used to select patients for this therapy.

There are no RCTs supporting the use of single-agent ICI in treatment-naïve patients. Randomised phase II data for atezolizumab vs. sunitinib showed a HR of 1.19 (95% CI: 0.82–1.71) which did not justify further assessment of atezolizumab as single agent as first-line treatment option in this group of patients, despite high complete response rates in the biomarker-positive population [509]. Single-arm phase II data for pembrolizumab from the KEYNOTE-427 trial show high response rates of 38% (up to 50% in PD-L1+ patients), but a PFS of 8.7 months (95% CI: 6.7–12.2) [509]. Based on these results and in the absence of randomised phase III data, single-agent checkpoint inhibitor therapy is not recommended as an alternative in a first-line therapy setting.

7.4.3.2 Immunotherapy/combination therapy

The phase III trial CheckMate 214 (NCT 02231749) showed a superiority of nivolumab and ipilimumab over sunitinib. The primary endpoint population focused on the IMDC intermediate- and poor-risk population where the combination demonstrated an OS benefit (HR: 0.63, 95% CI: 0.44–0.89) which led to regulatory approval [409] and a paradigm shift in the treatment of mRCC [1]. Results from CheckMate 214 further established that the combination of ipilimumab and nivolumab was associated with higher response rates (RR) (39% in the ITT population), complete response rates (8% in the ITT population [central radiology review]) and duration of response compared to sunitinib. Progression-free survival did not achieve the pre-defined endpoint. The exploratory analysis of OS data in the PD-L1-positive population was 0.45 (95% CI: 0.29–0.41).

A recent update with 60-month data shows ongoing benefits for the immune combination with independently assessed complete response rates of 11% and a HR for OS in the IMDC intermediate- and poor-risk group of 0.68 (0.58–0.81). The 60-months OS probability was 43% for ipilimumab plus nivolumab vs. 31% for sunitinib, respectively [510]. In this update the IMDC good-risk group did not continue to perform better with sunitinib although this effect occurs due to a late overlap of the KM-curves (HR for OS: 0.94 [95% CI: 0.65–1.37]) [511].

Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity including 1.5% treatment-related deaths. It should therefore be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multidisciplinary team (LE: 4). PD-L1 biomarker is currently not used to select patients for therapy.

The frequency of steroid use has generated controversy and further analysis, as well as real world data, are required. For these reasons the Panel continues to recommend ipilimumab and nivolumab in the intermediate- and poor-risk population.

The KEYNOTE-426 trial (NCT02853331 reported results for the combination of axitinib plus pembrolizumab vs. sunitinib in 861 treatment-naïve cc-mRCC patients [512]. Overall survival and PFS assessed by central independent review in the ITT population were the co-primary endpoints. Response rates and assessment in the PD-L1-positive patient population were secondary endpoints. With a median follow-up of 12.8 months, at first interim analysis both primary endpoints were reached, The median PFS in the pembrolizumab plus axitinib arm was 15.1 months vs. 11.1 in the sunitinib arm (HR: 0.69, 95% CI: 0.57–0.84, p < 0.001). Median OS has not been reached initially in either arm, but the risk of death was 47% lower in the axitinib plus pembrolizumab arm when compared to the sunitinib arm (OS HR: 0.53, 95% CI: 0.38–0.74, p < 0.0001). Response rates were also higher in the experimental arm (59.3% vs. 35.7%). Efficacy occurred irrespective of IMDC group and PD-L1 status. Treatment-related AEs (≥ grade 3) occurred in 63% of patients receiving axitinib and pembrolizumab vs. 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both arms.

A recent update of KEYNOTE-426 with a minimum follow-up of 35.6 months (median 42.8 months) demonstrated an ongoing OS benefit for axitinib plus pembrolizumab in the ITT population (HR: 0.73, 95% CI: 0.60–0.88, p < 0.001). Median OS for axitinib plus pembrolizumab was 45.7 months (95% CI: 43.6 – NR) vs. 40.1 month (95% CI: 34.3 – 44.2) for sunitinib with a PFS benefit (HR: 0.68, 95% CI: 0.58–0.80, p < 0.0001) which was across all IMDC subgroups for PFS, while OS was similar between axitinib plus pembrolizumab

vs. sunitinib in the favourable subgroup with an OS benefit in the IMDC intermediate- and poor-risk groups. The complete response rate by independent review was 10% in the pembrolizumab plus axitinib arm and 4% in the sunitinib arm [513].

The phase III CheckMate 9ER trial randomised 651 patients to nivolumab plus cabozantinib (n = 323) or vs. sunitinib (n = 328) in treatment-naïve cc-mRCC patients. The primary endpoint of PFS assessed by central independent review in the ITT population was significantly prolonged for nivolumab plus cabozantinib (16.6 months) vs. sunitinib (8.3 months, HR: 0.51, 95% CI: 0.41–0.64, p < 0.0001). The nivolumab/cabozantinib combination also demonstrated a significant OS benefit in the secondary endpoint compared with sunitinib (HR: 0.60, CI: 0.40–0.89, p = 0.0010) after a median follow-up of 18.1 months. The independently assessed ORR was 55.7% vs. 27.1% with a complete response rate of 8% for nivolumab plus cabozantinib vs. 4.6% with sunitinib. The efficacy was observed independent of IMDC group and PD-L1 status. Treatment-related AEs (≥ grade 3) occurred in 61% of patients receiving cabozantinib and nivolumab vs. 51% of patients receiving sunitinib. Treatment-related deaths occurred in one patient in the nivolumab/cabozantinib arm and in two patients in the sunitinib arm.

Recently, the randomised phase III trial CLEAR (Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma) was published [439]. CLEAR randomised a total of 1,069 patients (in a 1:1:1 ratio) to lenvatinib plus pembrolizumab (n = 355) vs. lenvatinib plus everolimus (n = 357) vs. sunitinib (n = 357). The trial reached its primary endpoint of independently assessed PFS at a median of 23.9 vs. 9.2 months, for lenvatinib plus pembrolizumab vs. sunitinib, respectively (HR: 0.39, 95% CI: 0.32–0.49, p < 0.001). Overall survival significantly improved with lenvatinib plus pembrolizumab vs. sunitinib (HR: 0.66, 95% CI: 0.49–0.88, p = 0.005). Objective response for lenvatinib plus pembrolizumab was 71% with 16% of the patients having a complete remission. Efficacy was observed across all IMDC risk groups, independently of PD-L1 status. Treatment-related AEs of grade 3 and higher with lenvatinib plus pembrolizumab were 72%. Treatment-related death occurred in four patients in the lenvatinib plus pembrolizumab arm and in one patient in the sunitinib arm.

The JAVELIN trial investigated 886 patients in a phase III RCT of avelumab plus axitinib vs. sunitinib [453]. The trial met one of its co-primary endpoints (PFS in the PD-L1-positive population at first interim analysis [median follow up 11.5 months]). Hazard ratios for PFS and OS in the ITT population were 0.69 (95% CI: 0.56–0.84) and 0.78 (95% CI: 0.55–1.08), respectively. The same applies to the atezolizumab/bevacizumab combination which also achieved a PFS advantage over sunitinib in the PD-L1-positive population at interim analysis and ITT (HR: 0.74, 95% CI: 0.57–0.96), but has not yet shown a significant OS advantage (HR: 0.81, 95% CI: 0.63–1.03) [514]. Final OS results are awaited and the combination cannot currently be recommended.

Table 7.4: First line immune checkpoint inhibitor combination trials for clear-cell RCC
Cross trial comparison is not recommended and should occur with caution

Study	N	Experimental arm	Primary endpoint	Risk groups	PFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
KEYNOTE-426 NCT02853331 Median follow-up 42,8 months [513, 515]	861	Pembrolizumab 200 mg. IV Q3W plus axitinib 5 mg. PO BID vs. sunitinib 50 mg PO QD 4/2 wk	PFS and OS in the ITT by BICR	**IMDC** FAV 31% IMD 56% POOR 13% **MSKCC** Not determined	(ITT) PEMBRO + AXI: 15.7 (13.6-20.2) SUN: 11.1 (8.9-12.5) HR: 0.68 (95% CI: 0.58, 0.8) p < 0.0001	(ITT) PEMBRO + AXI: 45.7 (43.6–NR) SUN: 40.1 (34.3-44.2) HR: 0.73 (95% CI: 0.60-0.88) p = 0.001
JAVELIN 101 NCT02684006 Median follow-up 19 months [453, 508]	886	Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BID vs. sunitinib 50 mg PO QD 4/2 wk	PFS in the PD-L1+ population and OS in the ITT by BICR	**IMDC** FAV 22% IMD 62% POOR 16% **MSKCC** FAV 23% IMD 66% POOR 12%	(PD-L1+) AVE + AXI: 13.8 (10.1-20.7) SUN: 7.0 (5.7-9.6) HR: 0.62 (95% CI: 0.49, 0.78) p < 0.0001	(PD-L1+) AVE + AXI: NR SUN: 28.6 (27.4-NE) HR: 0.83 (95% CI: 0.60-1.15) p = 0.1301

Immotion 151 **NCT02420821** Median follow-up 24 months [514]	915	Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cycle vs. sunitinib 50 mg. PO QD 4/2 wk	PFS in the PD-L1+ population and OS in the ITT by IR	**IMDC** Not determined **MSKCC** FAV 20% IMD 69% POOR 12%	(PD-L1+) ATEZO + BEV: 11.2 (8.9-15.0) SUN: 7.7 (6.8-9.7) HR: 0.74 (95% CI: 0.57, 0.96) p = 0.0217	(ITT) ATEZO + BEV: 33.6 (29.0-NE) SUN: 34.9 (27.8-NE) HR: 0.93 (95% CI: 0.76-1.14) p 0.4751
Checkmate 214 **NCT02231749** Median follow-up of 60 months [451, 511]	1096	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W vs. sunitinib 50 mg. PO QD 4/2 wk	PFS and OS in the IMDC inter-mediate and poor population by BICR	**IMDC** FAV 23% IMD 61% POOR 17% **MSKCC** Not determined	(IMDC IMD/poor) NIVO + IPI: 11.6 (8.4-16.5) SUN: 8.3 (7.0-10.4) HR: 0.73 (95% CI: 0.61, 0.87)	(IMDC IMD/poor) NIVO + IPI: 47.0 (35.4-57.4) SUN: 26.6 (22.1-33.5) HR: 0.68 (0.58-0.81) p < 0.0001
CheckMate 9ER **NCT03141177** Median follow-up of 23.5 months [452, 516]	651	Nivolumab 240 mg fixed dose IV every 2 wk plus cabozantinib 40 mg PO daily vs. sunitinib 50 mg PO QD 4/2 wk	PFS in the ITT by BICR	**IMDC** FAV 22% IMD 58% POOR 20% **MSKCC** Not determined	(ITT) NIVO + CABO: 17.0 (12.6–19.4) SUN: 8.3 (6.9–9.7) HR: 0.52 (95% CI: 0.43–0.64) p < 0.0001	(ITT) NIVO + CABO: NR (NE) SUN: 29.5 (28.4–NE) HR: 0.66 (98.9% CI: 0.50-0.87) p = 0.0034
CLEAR **NCT02811861** Median follow-up of 33.4 months [439, 517]	712	Pembrolizumab 200 mg IV Q3W plus lenvatinib 20 mg PO QD vs. sunitinib 50 mg PO QD 4/2 wk	PFS in the ITT by BIRC	**IMDC** FAV 31% IMD 59% POOR 9% NE 1% **MSKCC** FAV 27% IMD 64% POOR 9%	(ITT) PEMBRO + LEN: 23.9 (20.8-27.7) SUN: 9.2 (6.0-11.0) HR: 0.39 (95% CI: 0.32-0.49) p > 0.001	(ITT) PEMBRO + LEN: NR (41.5–NE) SUN: NR (38.4–E) HR: 0.72 (95% CI: 0.55–0.93) p = 0.005

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central review; BID = twice a day; CABO = cabozantinib; CI = confidence interval; FAV = favourable; R = hazard ratio; IPI = ipilimumab; IMD = intermediate; IMDC = Metastatic Renal Cancer Database Consortium; IR = investigator review; ITT = intention-to-treat; IV = intravenous; LEN = lenvatinib; mo = months; MSKCC = Memorial Sloan Kettering Cancer Center; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; PO = by mouth; BID = twice a day; QD = once a day; Q2W = every 2 weeks; Q3W = every 3 weeks; SUN = sunitinib; wk = weeks.

Patients who stop nivolumab plus ipilimumab because of toxicity require expert guidance and support from a multi-disciplinary team before re-challenge can occur (LE: 1). Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible (LE: 4).

Treatment past progression with nivolumab plus ipilimumab can be justified but requires close scrutiny and the support of an expert multi-disciplinary team [514, 518] (LE: 1).

Patients who stop TKI and IO due to immune-related toxicity can receive single-agent TKI once the adverse event has resolved (LE: 1). Adverse event management, including transaminitis and diarrhoea, require particular attention as both agents may be causative. Expert advice should be sought on re-challenge of ICIs after significant toxicity (LE: 4). Treatment past progression on axitinib plus pembrolizumab or nivolumab plus cabozantinib requires careful consideration as it is biologically distinct from treatment past progression on ipilimumab and nivolumab.

Generally, the Panel is of the opinion that nivolumab plus ipilimumab, pembrolizumab plus axitinib and nivolumab plus cabozantinib should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multi-disciplinary team (LE: 4).

*7.4.4 **Therapeutic strategies***

7.4.4.1 Treatment-naïve patients with clear-cell metastatic RCC

The combination of pembrolizumab plus axitinib as well as nivolumab plus cabozantinib and lenvatinib plus pembrolizumab is the standard of care in all IMDC-risk patients and ipilimumab plus nivolumab in IMDC intermediate- and poor-risk patients (Figure 7.1). Therefore, the role of VEGFR-TKIs alone in front-line mRCC has been superseded. Sunitinib, pazopanib, and cabozantinib (IMDC intermediate- and poor-risk disease), remain alternative treatment options for patients who cannot receive or tolerate immune checkpoint inhibition in this setting (Figure 7.1).

7.4.4.1.1 Sequencing systemic therapy in clear-cell metastatic RCC

The sequencing of targeted therapies is established in mRCC and maximises outcomes [498, 507]. Pembrolizumab plus axitinib, nivolumab plus cabozantinib, lenvatinib plus pembrolizumab and nivolumab plus ipilimumab are the new standard of care in front-line therapy. The impact of front-line immune checkpoint inhibition on subsequent therapies is unclear. Randomised data on patients with disease refractory to either nivolumab plus ipilimumab or TKI plus IO in a first-line setting are lacking, and available cohorts are limited [519]. Prospective data on tivozanib, cabozantinib and axitinib are available for patients progressing on immunotherapy, but these studies do not focus solely on the front-line setting, involve subset analyses, and are too small for definitive conclusions [507, 520].

Retrospective data on VEGFR-TKI therapy after progression on front-line immune combinations exist but have significant limitations. When considering this data in totality, there is some activity but it is still too early to recommend one VEGFR-TKI over another after immunotherapy/immunotherapy or immunotherapy/VEGFR combination (Figure 7.2). After the axitinib plus pembrolizumab combination, changing the VEGFR-TKI at progression to cabozantinib or any other TKI not previously used is recommended.

The Panel do not support the use of mTOR inhibitors unless VEGF-targeted therapy is contraindicated as they have been outperformed by other VEGF-targeted therapies in mRCC [521]. Drug choice in the third-line setting, after ICI combinations and subsequent VEGF-targeted therapy, is unknown. The Panel recommends a subsequent agent which is approved in VEGF-refractory disease, with the exception of re-challenge with immune checkpoint blockade. Cabozantinib is the only agent in VEGF-refractory disease with RCT data showing a survival advantage and should be used preferentially [468]. Axitinib has positive PFS data in VEGF-refractory disease. Both sorafenib and everolimus have been outperformed by other agents in VEGF-refractory disease and are therefore less attractive [521]. The lenvatinib plus everolimus combination appears superior to everolimus alone and has been granted EMA regulatory approval based on randomised phase II data. This is an alternative despite the availability of phase II data only [498]. As shown in a study which also included patients on ICIs tivozinib provides PFS superiority over sorafenib in VEGF-refractory disease [522].

7.4.4.1.2 Summary of evidence and recommendations for immunotherapy in cc-mRCC

Summary of evidence	**LE**
Treatment-naïve patients	
Currently, PD-L1 expression is not used for patient selection.	2b
The combination of nivolumab and ipilimumab in treatment-naïve patients with cc-mRCC of IMDC intermediate- and poor risk demonstrated OS and ORR benefits compared to sunitinib.	1b
The combination of pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab plus cabozantinib in treatment-naïve patients with cc-mRCC across all IMDC risk group demonstrated PFS, OS and ORR benefits compared to sunitinib.	1b
Nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib and lenvatinib plus pembrolizumab should be administered in centres with experience of immune combination therapy and appropriate supportive care within the context of a multi-disciplinary team.	4
The combination of nivolumab plus ipilimumab in the IMDC intermediate- and poor-risk population of treatment-naïve patients with cc-mRCC leads to superior survival compared to sunitinib.	2b
Sequencing systemic therapy	
Nivolumab leads to superior OS compared to everolimus in disease progression after one or two lines of VEGF-targeted therapy.	1b
Axitinib, cabozantinib or lenvatinib can be continued if immune-related AEs result in cessation of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab. Re-challenge with immunotherapy requires expert support.	4

Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible. Re-challenge with combination therapy requires expert support.	4
Treatment past progression can be justified but requires close scrutiny and the support of an expert multi-disciplinary team.	1b
Nivolumab plus ipilimumab was associated with 15% grade 3-5 toxicity and 1.5% treatment-related deaths. Tyrosine kinase inhibitor-based IO combination therapies were associated with grade 3-5 toxicity ranging between 61-72% and 1% of treatment-related deaths.	1b

Recommendations	**Strength rating**
Treatment-naïve patients	
Offer nivolumab or cabozantinib for immune checkpoint inhibitor-naive vascular endothelial growth factor receptor (VEGFR)-refractory clear-cell metastatic renal cell carcinoma (cc-mRCC) after one or two lines of therapy.	Strong
Offer ipilimumab plus nivolumab to treatment-naive patients with IMDC intermediate- and poor-risk cc-mRCC.	Strong
Administer nivolumab plus ipilimumab, pembrolizumab plus axitinib, lenvatinib plus pembrolizumab and nivolumab and cabozantinib in centres with experience of immune combination therapy and appropriate supportive care within the context of a multi-disciplinary team.	Weak
Offer sunitinib or pazopanib to treatment-naïve patients with IMDC favourable-, intermediate-, and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong
Offer cabozantinib to treatment-naïve patients with IMDC intermediate- and poor-risk cc-mRCC who cannot receive or tolerate immune checkpoint inhibition.	Strong[a]
Patients who do not receive the full four doses of ipilimumab due to toxicity should continue on single-agent nivolumab, where safe and feasible.	Weak
Sequencing systemic therapy	
Offer axitinib, cabozantinib or lenvatinib as subsequent treatment to patients who experience treatment-limiting immune-related adverse events after treatment with the combination of axitinib plus pembrolizumab, cabozantinib plus nivolumab or lenvatinib plus pembrolizumab.	Weak
Treatment past progression can be justified but requires close scrutiny and the support of an expert multi-disciplinary team.	Weak
Do not re-challenge patients who stopped immune checkpoint inhibitors because of toxicity without expert guidance and support from a multi-disciplinary team.	Strong

[a] *While this is based on a randomised phase II trial, cabozantinib (weak) looks at least as good as sunitinib in this population. This justified the same recommendation under exceptional circumstances.*

Figure 7.1: Updated EAU Guidelines recommendations for the first-line treatment of cc-mRCC

	Standard of Care	Alternative in patients who can not receive or tolerate immune checkpoint inhibitors
IMDC favourable risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b]	sunitinib* [1b] pazopanib* [1b]
IMDC intermediate and poor risk	nivolumab/cabozantinib [1b] pembrolizumab/axitinib [1b] pembrolizumab/lenvatinib [1b] nivolumab/ipilimumab [1b]	cabozantinib* [2a] sunitinib*[1b] pazopanib* [1b]

IMDC = The International Metastatic Renal Cell Carcinoma Database Consortium.
**pazopanib for intermediate-risk disease only.*
[1b] = based on one randomised controlled phase III trial.
[2a] = based on a well-designed study without randomisation, or a subgroup analysis of a randomised controlled trial.

Figure 7.2: EAU Guidelines recommendations for later-line therapy

	Standard of care	Alternative
Prior IO	Any VEGF-targeted therapy that has not been used previously in combination with IO [4]	
Prior TKI	nivolumab [1b] cabozantinib [1b]	axitinib [2b]

IO = immunotherapy; TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor.
[1b] = based on one randomised controlled phase III trial.
[2b] = subgroup analysis of a randomised controlled phase III trial.
[4] = expert opinion.

7.4.4.1.3 Renal tumours with sarcomatoid features

Subset analyses have shown improved results for PD-L1 inhibitors combined with CTLA4 or VEGF-targeted therapy in renal tumours with sarcomatoid features. Bevacizumab/atezolizumab, ipilimumab/nivolumab, axitinib/pembrolizumab and avelumab/axitinib can all be recommended instead of VEFG-targeted therapy alone. These options have OS advantages over sunitinib and superseded VEGF-targeted therapy.

Table 7.5: Subgroup analysis of first-line immune checkpoint inhibitor combinations in RCC patients with sarcomatoid histology

Cross trial comparison is not recommended and should occur with caution

Study	N (ITT)	Therapy	N (sRCC)	PFS (mo.) Median (95% CI) HR	OS (mo.) Median (95% CI) HR	ORR (%) (95% CI)
KEYNOTE-426 NCT02853331 Median follow-up 12,8 months [523]	861	PEMBRO + AXI SUN	51 54	NR 8.4 HR: 0.54 (0.29-1.00)	NR NR HR: 0.58 (0.21-1.59)	58.8 31.5
JAVELIN 101 NCT02684006 [524]	886	AVE+AXI SUN	47 61	7.0 (5.3-13.8) 4.0 (2.7-5.7) HR 0.57 (0.33-1.00)	NA	46.8 (32.1-61.9) 21.3 (11.9-33.7)
Immotion 151 NCT02420821 Median follow-up 13 to 17 mo. [525]	915	ATEZO+BEV SUN	68 74	8.3 (5.4, 12.9) 5.3 (3.3, 6.7) HR: 0.52 (0.34-0.79)	21.7 (15.3, NE) 15.4 (10.4, 19.5) 0.64 (0.41, 1.01)	49 (36-1) 14 (7-23)
Checkmate 214 NCT02231749 Median follow-up of 30 months [526]	1096	NIVO+IPI SUN	60 52	8.4 (5.2-24.0) 4.9 (4.0-7.0) HR: 0.61 (0.38-0.97)	31.2 (23.0-NE) 13.6 (7.7-20.9) HR: 0.55 (0.33-0.90)	56.7 (43.2-69.4) 19.2 (9.6-32.5)
CheckMate 9ER NCT03141177 Median follow-up 16 months [516]	651	NIVO+CABO SUN	34 41	10.3 (5.6-19.4) 4.2 (2.6-8.3) HR: 0.42 (0.23-0.74)	NR (22.8-NE) 19.7 (8.9–29.5) HR: 0.36 (0.17-0.79)	55.9 (37.9-72.8) 22.0 (10.6-37.6)
CLEAR NCT02811861 Median follow-up 27 months [439, 517]	712	PEMBRO+LEN SUN	28 21	11.1 5.5 HR: 0.39 (0.18-0.84)	NE NE HR: 0.91 (0.32–2.58)	60.7 23.8

ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; CABO = cabozantinib; CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; ITT = intention-to-treat; mo = months; NA = not available; NE = non-estimable; NR = not reached; NIVO = nivolumab; OS = overall survival; PEMBRO = pembrolizumab; PFS = profession-free survival; sRCC = sarcomatoid RCC; SUN = sunitinib.

7.4.4.1.3.1 Summary of evidence and recommendation for targeted therapy in RCC with sarcomatoid features

Summary of evidence	LE
Immune checkpoint inhibitor combination therapy was superior to sunitinib in terms of PFS and OS in trial subset analysis of clear-cell RCC with sarcomatoid features.	2a

Recommendation	Strength rating
Offer immune checkpoint inhibitor combination therapy for advanced cc-mRCC with sarcomatoid features.	Weak

7.4.4.2 Treatment of patients with non-clear-cell metastatic RCC

No phase III trials of patients with non-cc-mRCC have been reported. Expanded access programmes and subset analyses from RCC studies suggest the outcome of these patients with targeted therapy is poorer than for ccRCC. Targeted treatment in non-cc-mRCC has focused on temsirolimus, everolimus, sorafenib, sunitinib and pembrolizumab [528-531].

7.4.4.2.1 Summary of evidence and recommendation for targeted therapy in non-clear-cell metastatic RCC

Summary of evidence	LE
Both mTOR inhibitors and VEGF-targeted therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncological outcomes for sunitinib over everolimus.	2a
In non-cc-mRCC, sunitinib improved PFS over everolimus in a systematic review of phase II trials and subgroups of patients.	2a

Recommendation	Strength rating
Offer sunitinib to patients with other non-cc RCC subtypes than papillary RCC.	Weak

7.4.4.3 Papillary metastatic RCC

The most common non-cc subtypes are type I and non-type I pRCCs. There are small single-arm trials for sunitinib and everolimus [9, 531-534]. A trial of both types of pRCC treated with everolimus (RAPTOR), showed a median PFS of 3.7 months per central review in the ITT population with a median OS of 21.0 months [534]. In a non-randomised phase II trial, type 2 pRCC associated with HLRCC, a familial cancer syndrome caused by germline mutations in the fumarate hydratase enzyme gene, the combination of bevacizumab 10 mg/kg IV every two weeks and erlotinib 150 mg orally daily has been evaluated [535]. The combination regimen reports interesting activity with an ORR of 64% (27/42, 95% CI: 49–77) in the HLRCC cohort, with a median PFS of 21.1 months (95% CI: 15.6–26.6). Grade ≥ 3 treatment-related AEs occurred in 47% of patients, including hypertension (34%) and proteinuria (13%).

For pRCC new evidence is available from the SWOG PAPMET randomised phase II trial which compared sunitinib to cabozantinib, crizotinib and savolitinib in 152 patients with papillary mRCC [536]. Progression-free survival was longer in patients in the cabozantinib group (median 9.0 months, 95% CI: 6–12) than in the sunitinib group (5.6 months, CI: 3–7; HR for progression or death 0.60 [0.37–0.97, one-sided p = 0.019]). Response rate for cabozantinib was 23% vs. 4% for sunitinib (two-sided p = 0.010). Savolitinib and crizotinib did not improve PFS compared with sunitinib. Grade 3 or 4 AEs occurred in 69% (31/45) of patients receiving sunitinib, 74% (32/43) of patients receiving cabozantinib, 37% (10/27) receiving crizotinib, and 39% (11/28) receiving savolitinib; one grade 5 thromboembolic event was recorded in the cabozantinib group. These results support adding cabozantinib as an option for patients with papillary mRCC based on superior PFS results compared to sunitinib.

In addition, savolitinib was investigated in the SAVOIR trial [537] as first-line treatment for MET-driven tumours defined as chromosome 7 gain, MET amplification, MET kinase domain variations or hepatocyte growth factor amplification by DNA alteration analysis (~30% of screened patients were MET positive). In a limited patient group, savolitinib (n = 27) was compared with sunitinib (n = 33). The trial was stopped early, largely due to poor accrual. The efficacy data appeared to favour savolitinib (median PFS 7.0 months, 95% CI: 2.8 months-NR vs. 5.6 months, 95% CI: 4.1–6.9 months, PFS HR: 0.71, 95% CI: 0.37–1.36, OS HR: 0.51,94% CI: 0.21–1.17, RR: 27% vs. 7%, for savolitinib and sunitinib, respectively). The median OS for savolitinib was NR. Savolitinib was better tolerated compared with sunitinib with 42% grade ≥ 3 AEs compared to 81% with sunitinib.

Efficacy for pembrolizumab in the pRCC subset (118/165) was; RR: 29%, PFS: 5.5 months (95% CI: 3.9–6.1 months) and OS: 31.5 months (95% CI: 25.5 months-NR), but these results are based on a single-arm phase II study [509]. Pembrolizumab can be conceded in this setting due to the high unmet need.

Patients with non-cc-mRCC should be referred to a clinical trial, where appropriate

7.4.4.3.1 Summary of evidence and recommendation for targeted therapy in non-clear-cell metastatic RCC

Summary of evidence	LE
Cabozantinib improved PFS over sunitinib in patients with advanced pRCC without additional molecular testing.	2a
Savolitinib improved PFS over sunitinib in patients with MET-driven advanced pRCC.	2a
Pembrolizumab resulted in long-term median OS in a single-arm study in the pRCC subgroup.	2a

Recommendations	Strength rating
Offer cabozantinib to patients with advanced papillary RCC (pRCC) without molecular testing.	Weak
Offer savolitinib to patients with MET-driven advanced pRCC.	Weak
Offer pembrolizumab to patients with advanced pRCC without molecular testing.	Weak

7.4.4.4 Treatment of patients with rare tumours

7.4.4.4.1 Renal medullary carcinoma

Renal medullary carcinoma is one of the most aggressive RCCs [26, 27] and most patients (~67%) will present with metastatic disease [26, 28]. Even patients who present with seemingly localised disease may develop macrometastases shortly thereafter, often within a few weeks.

Despite treatment, median OS is thirteen months in the most recent series [33]. Due to the infiltrative nature and medullary epicentre of RMC, RN is favoured over PN even in very early-stage disease. Retrospective data indicate that nephrectomy in localised disease results in superior OS (16.4 vs. 7 months) compared with systemic chemotherapy alone, but longer survival was noted in patients who achieved an objective response to first-line chemotherapy [33, 538]. There is currently no established role for distant metastasectomy or nephrectomy in the presence of metastases.

Palliative radiation therapy is an option and may achieve regression in the targeted areas but it will not prevent progression outside the radiation field [539, 540]. Renal medullary carcinoma is refractory to monotherapies with targeted anti-angiogenic regimens including TKIs and mTOR inhibitors [33, 165]. The mainstay systemic treatments for RMC are cytotoxic combination regimens which produce partial or complete responses in ~29% of patients [165]. There are no prospective comparisons between different chemotherapy regimens but most published series used various combinations of platinum agents, taxanes, gemcitabine, and/or anthracyclines [33, 34]. High-dose-intensity combination of MVAC has also shown efficacy against RMC [541] although a retrospective comparison did not show superiority of MVAC over cisplatin, paclitaxel, and gemcitabine [34]. Single-agent anti-PD-1 immune checkpoint therapy has produced responses in a few case reports, although, as yet, insufficient data are available to determine the response rate to this approach [539, 540]. Whenever possible, patients should be enrolled in clinical trials of novel therapeutic approaches, particularly after failing first-line cytotoxic chemotherapy.

7.4.4.5 Treatment of hereditary RCC

7.4.4.5.1 von-Hippel-Lindau-disease-associated RCC

Patients with VHL disease often develop RCC and tumours in other organs including CNS, retinal haemangioblastomas, and pancreatic tumours, and commonly undergo several surgical resections in their lifetime. In VHL disease, belzutifan, a hypoxia-inducible factor 2α (HIF-2α) inhibitor, has been approved by the US Food and Drug Administration (FDA) for the treatment of ccRCC and other neoplasms associated with VHL for the treatment of tumours that do not require immediate surgery. Approval was based on the results from a phase II, open-label, single-arm trial in patients with tumours not larger than 3 cm [542]. Belzutifan induced partial responses with an RCC ORR of 49%, and a disease control rate of 98.4% after 21.8 months treatment. All patients with pancreatic lesions had an ORR of 77%, and those with CNS haemangioblastoma had a 30% response rate. In total, 33% of patients reported ≥ grade 3 AEs, and seven patients (11.5%) discontinued the treatment. In the treatment with pazopanib for VHL only 52% continued with the treatment after 24 weeks [543].

With favourable efficacy results and with relatively low-grade side effects, belzutifan seems to be a valuable contribution to the treatment of patients with the VHL disease, and it is currently under review by the EMA.

7.5 Locally recurrent RCC after treatment of localised disease

Most studies reporting on local recurrent disease after removal of the kidney have not considered the true definition of local recurrence after RN, PN and thermal ablation, which are: local recurrence in the tumour-bearing kidney, tumour growth exclusively confined to the true renal fossa, recurrences within the renal vein,

the ipsilateral adrenal gland or the regional LNs. In the existing literature the topic is weakly investigated and often regarded as local recurrent disease.

7.5.1 Locally recurrent RCC after nephron-sparing approaches

Locally recurrent disease can affect the tumour-bearing kidney after PN or focal ablative therapy such as RFA and cryotherapy. Local relapse may be due to the incomplete resection of the primary tumour, in a minority of the cases to the local spread of the tumour by microvascular embolisation, or true multifocality [203, 544].

The prognosis of recurrent disease not due to multifocality is poor, despite salvage nephrectomy [544]. Recurrent tumour growth in the regional LNs or ipsilateral adrenal gland may reflect metachronous metastatic spread (see Section 7.3). After treatment solely for localised disease, systemic progression is common [545, 546].

Following thermal ablation or cryotherapy generally intra-renal, but also peri-renal, recurrences have been reported in up to 14% of cases [547]. Whereas repeat ablation is still recommended as the preferred therapeutic option after treatment failure, the most effective salvage procedure as an alternative to complete nephrectomy has not yet been defined.

7.5.2 Locally recurrent RCC after radical nephrectomy

Isolated local fossa recurrence is rare and occurs in about 1-3% after radical nephrectomy. More commonly in pT3-4 than pT1-2 and grade 3-4. Most patients with local recurrence of RCC are diagnosed by either CT/MRI scans as part of the post-operative follow-up [548]. The median time to recurrence after RN was 19-36 months in isolated local recurrence or 14.5 months in group including metastatic cases as well [548-550].

Isolated local recurrence is associated with worse survival [203, 551]. Based on retrospective and non-comparative data only, several approaches such as surgical excision, radiotherapy, systemic treatment and observation have been suggested for the treatment of isolated local recurrence [552-554]. Among these alternatives, surgical resection with negative margins remains the only therapeutic option shown to be associated with improved survival [551]. Open surgery has been successfully reported in studies [555, 556]. One of the largest series including 2,945 patients treated with RN reported on 54 patients with recurrent disease localised in the renal fossa, the ipsilateral adrenal gland or the regional LNs as sole metastatic sites [552]. Another recent series identified 33 patients with isolated local recurrences and 30 local recurrences with synchronous metastases within a cohort of 2,502 surgically treated patients, confirming the efficacy of locally directed treatment vs. conservative approaches (observation, systemic therapy) [557].

A five-year OS with isolated local recurrence was 60% (95% CI: 0.44–0.73) and ten-year OS was 32% (95% CI: 0.15–0.51). Overall survival differed significantly by the time period between primary surgery and occurrence of recurrence (< two years vs. ≥ two years: ten-year OS rate 31% (95% CI: 10.2–55.0) vs. 45% (95% CI: 21.5–65.8; HR: 0.26; p = 0.0034) [548]. Metastatic progression was observed in 60 patients (58.8%) after surgery [549]. Patient survival can be linked to the type of treatment received, as shown by Marchioni, et al. In a cohort of 96 patients, 45.8% were metastatic at the time of recurrence; three-year CSS rates after local recurrence were 92.3% (± 7.4%) for those who were treated with surgery and systemic therapy, 63.2% (± 13.2%) for those who only underwent surgery, 22.7% (± 0.9%) for those who only received systemic therapy and 20.5% (± 10.4%) for those who received no treatment (p < 0.001).

However, minimally invasive approaches, including standard and hand-assisted laparoscopic- and robotic approaches for the resection of isolated RCC recurrences have been occasionally reported. Recently, Martini *et al.,* published the largest surgical cohort of robotic surgery in this setting (n = 35) providing a standardisation of the nomenclature, describing the surgical technique for each scenario and reporting on complications, renal function, and oncologic outcomes [558]. Ablative therapies including cryoablation, radiofrequency and microwave ablation, may also have a role in managing recurrent RCC patients, but further validation will be needed [559, 560].

In summary, the limited available evidence suggests that in selected patients surgical removal of locally recurrent disease with negative margins can induce durable tumour control, although with expected high risk of complications. Johnson *et al.* published on 51 planned repeat PNs in 47 patients with locally recurrent disease, reporting a total of 40 peri-operative complications, with temporary urinary extravasation being the most prevalent [561]. Since local recurrences develop early, with a median time interval of 10–20 months after treatment of the primary tumour [562], a guideline-adapted follow-up scheme for early detection is recommended (see Chapter 8 - Follow-up) even though benefit in terms of cancer control has not yet been demonstrated [563].

Adverse prognostic parameters are a short time interval since treatment of the primary tumour (< 3–12 months) [564], sarcomatoid differentiation of the recurrent lesion and incomplete surgical resection [552]. In case

complete surgical removal is unlikely to be performed or when significant comorbidities are present (especially when combined with poor prognostic tumour features), palliative therapeutic approaches including radiation therapy aimed at symptom control and prevention of local complications should be considered (see Sections 7.3 and 7.4).

Following metastasectomy of local recurrence after nephrectomy, adjuvant therapy can be considered (see Section 7.2.5. Neoadjuvant and adjuvant therapy). Local recurrence combined with other metastases is treated as a metastatic RCC.

7.5.3 Summary of evidence and recommendation on locally recurrent RCC after treatment of localised disease

Summary of evidence	LE
Isolated recurrence after nephron-sparing procedures or nephrectomy is a rare entity (< 2%).	3
Surgical or percutaneous treatment of local recurrences in absence of systemic progression should be considered, especially in absence of adverse prognostic parameters and favourable performance status.	3
The most optimal modality of local treatment for locally recurrent RCC after nephron-sparing procedures or nephrectomy is not defined.	3

Recommendation	Strength rating
Offer local treatment of locally recurrent disease when technically possible and after balancing adverse prognostic features, comorbidities and life expectancy.	Weak

8. FOLLOW-UP IN RCC

8.1 Introduction

Surveillance after treatment for RCC allows the urologist to monitor or identify:

- post-operative complications;
- renal function;
- local recurrence;
- recurrence in the contralateral kidney;
- distant metastases;
- cardiovascular events.

There is no consensus on follow-up strategies after RCC treatment, with limited evidence suggesting that more frequent post-operative imaging intervals do not provide any improvement for early detection of recurrence that would lead to improved survival [563]. As such, intensive radiological surveillance may not be necessary for all patients. Follow-up is also important to assess functional outcomes and to limit long-term sequelae such as renal function impairment, end-stage renal disease and cardiovascular events [565].

Currently, the key question is whether any recurrence detection during follow-up and subsequent treatment will lead to any meaningful change in survival outcome for these patients.

In contrast to high-grade and/or locally advanced disease, the outcome after surgery for T1a low-grade tumours is almost always excellent. It is therefore reasonable to stratify follow-up, taking into account the risk of each different RCC to develop a local or distant recurrence. Although there is no randomised evidence, large studies have examined prognostic factors with long follow-up [188, 566, 567] (LE: 4). One study has shown a survival benefit in patients who were followed within a structured surveillance protocol vs. patients who were not [568]; patients undergoing follow-up seem to have a longer OS when compared to patients not undergoing routine follow-up [568].

Furthermore, an individualised and risk-based approach to RCC follow-up has recently been proposed. The authors used competing risk models, incorporating patient age, pathologic stage, relapse location and comorbidities, to calculate when the risk of non-RCC death exceeds the risk of RCC recurrence [569]. For patients with low-stage disease but with a Charlson comorbidity index ≥ 2, the risk of non-RCC death exceeded that of abdominal recurrence risk already one month after surgery, regardless of patient age.

The RECUR consortium, initiated by this Panel, collects similar data with the aim to provide comparators for guideline recommendations. Recently published RECUR data support a risk-based approach; more specifically a competing-risk analysis showed that for low-risk patients, the risk of non-RCC related death exceeded the risk of RCC recurrence shortly after the initial surgery. For intermediate-risk patients, the corresponding time point was reached around four to five years after surgery. In high-risk patients, the risk of RCC recurrence continuously exceeded the risk of non-RCC related death [10]. In the near future, genetic profiling may refine the existing prognostic scores and external validation in datasets from adjuvant trials have been promising in improving stratification of patient's risk of recurrence [10, 570].

Recurrence after PN is rare, but early diagnosis is relevant, as the most effective treatment is surgery [555, 571]. Recurrence in the contralateral kidney is rare (1–2%) and can occur late (median 5–6 years) [572] (LE: 3). Follow-up can identify local recurrences or metastases at an early stage. In metastatic disease, extended tumour growth can limit the opportunity for surgical resection, which is considered the standard therapy in cases of resectable and preferably solitary lesions. In addition, early diagnosis of tumour recurrence may enhance the efficacy of systemic treatment if the tumour burden is low.

8.2 Which imaging investigations for which patients, and when?

- The sensitivity of chest radiography and US for detection of small RCC metastases is poor. The sensitivity of chest radiography is significantly lower than CT-scans, as proven in comparative studies including histological evaluation [573-575]. Therefore, follow-up for recurrence detection with chest radiography and US are less sensitive [576].
- Positron-emission tomography and PET-CT as well as bone scintigraphy should not be used routinely in RCC follow-up, due to their limited specificity and sensitivity [6, 127].
- Surveillance should also include evaluation of renal function and cardiovascular risk factors [565].
- Outside the scope of regular follow-up imaging of the chest and abdomen, targeted imaging should be considered in patients with organ-specific symptoms, e.g., CT or MRI imaging of the brain in patients experiencing neurological symptoms [577].

Controversy exists on the optimal duration of follow-up. Some authors argue that follow-up with imaging is not cost-effective after five years; however, late metastases are more likely to be solitary and justify more aggressive therapy with curative intent. In addition, patients with tumours that develop in the contralateral kidney can be treated with NSS if the tumours are detected early. Several authors have designed scoring systems and nomograms to quantify the likelihood of patients to develop tumour recurrences, metastases, and subsequent death [238, 240, 578, 579]. These models, of which the most utilised are summarised in Chapter 6 - Prognosis, have been compared and validated [580] (LE: 2). Using prognostic variables, several stage-based follow-up regimens have been proposed, although, none propose follow-up strategies after ablative therapies [581, 582]. A post-operative nomogram is available to estimate the likelihood of freedom from recurrence at five years [235]. Recently, a pre-operative prognostic model based on age, symptoms and TNM staging has been published and validated [583] (LE: 3).

A follow-up algorithm for monitoring patients after treatment for RCC is needed, recognising not only the patient's risk of recurrence profile, but also the efficacy of the treatment given (Table 8.1). These prognostic systems can be used to adapt the follow-up schedule according to predicted risk of recurrence. Ancillary to the above, life-expectancy calculations based on comorbidity and age at diagnosis may be useful in counselling patients on duration of follow-up [584].

Table 8.1: Proposed follow-up schedule following treatment for localised RCC, taking into account patient risk of recurrence profile and treatment efficacy (based on expert opinion [LE: 4])

Risk profile (*)	**Oncological follow-up after date of surgery**								
	3 mo	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**30 mo**	**36 mo**	**> 3 yr (**) (***)**	**> 5 yr (**) (***)**
Low risk of recurrence <u>For ccRCC:</u> Leibovich Score 0-2 <u>For non-ccRCC:</u> pT1a-T1b pNx-0 M0 and histological grade 1 or 2.	-	CT	-	CT	-	CT	-	CT once every two yrs	-

Intermediate risk of recurrence <u>For ccRCC:</u> Leibovich Score 3-5 <u>For non-ccRCC:</u> pT1b pNx-0 and/or histological grade 3 or 4.	-	CT	CT	-	CT	-	CT	CT once yr	CT once every two yrs
High risk of recurrence <u>For ccRCC:</u> Leibovich Score ≥ 6 <u>For non-ccRCC:</u> pT2-pT4 with any histological grade or pT any, pN1 cM0 with any histological grade	CT	CT	CT	CT	CT	-	CT	CT once yr	CT once every two yrs

ccRCC = clear cell renal cell carcinoma; CT = computed tomography; mo = months; non-ccRCC = non clear cell renal cell carcinoma; yr = years.

The table above provides recommendations on follow-up strategies for low, intermediate and high risk of recurrence in patients curatively treated for localised RCC either with NSS or RN. Computed tomography in the table refers to imaging of both chest and abdomen. Alternatively, MRI of the abdomen can be performed instead of a CT-scan.

* *Risk of recurrence profiles should be based on validated prognostic models. The EAU RCC Guidelines Panel recommends the 2003 Leibovich model for ccRCC [238]. However, other validated models can be used by physicians based on their own national/regional recommendations. In a similar fashion, for curatively treated localised non-ccRCC, the Panel recommends the use of the University of California Los Angeles integrated staging system (UISS) to determine risk of recurrence [239].*

** *For all risk of recurrence profiles, functional follow-up, mainly monitoring renal and cardiovascular function, may continue according to specific clinical needs irrespective of the length of the oncological follow-up.*

*** *For low-risk profiles at > 3 years and intermediate-risk at > 5 years of follow-up respectively, consider counselling patients about terminating oncological follow-up imaging based on assessment of comorbidities, age, life expectancy and/or patient wishes.*

8.3 Summary of evidence and recommendations for surveillance following RN or PN or ablative therapies in RCC

Summary of evidence	LE
Functional follow-up after curative treatment for RCC is useful to prevent renal and cardiovascular deterioration.	4
Oncological follow-up can detect local recurrence or metastatic disease while the patient may still be surgically curable.	4
After NSS, there is an increased risk of recurrence for larger (> 7 cm) tumours, or when there is a positive surgical margin.	3
Patients undergoing follow-up have a better OS than patients not undergoing surveillance.	3
Prognostic models provide stratification of RCC risk of recurrence based on TNM and histological features.	3
In competing-risk models, risk of non-RCC-related death exceeds that of RCC recurrence or related death in low-risk patients.	3
Life expectancy estimation is feasible and may support counselling of patients on duration of follow-up.	4

Recommendations	Strength rating
Base follow-up after treatment of localised RCC on the risk of recurrence.	Strong
Perform functional follow-up (renal function assessment and prevention of cardiovascular events) both in nephron-sparing (NSS) and radical nephrectomy patients.	Weak
Intensify follow-up in patients after NSS for tumours > 7 cm or in patients with a positive surgical margin.	Weak
Consider curtailing follow-up when the risk of dying from other causes is double that of the RCC recurrence risk.	Weak
Base risk of recurrence stratification on validated subtype-specific models such as the Leibovich Score for ccRCC or the University of California Los Angeles integrated staging system for non-ccRCC.	Weak

8.4 Research priorities

There is a clear need for future research to determine whether follow-up can optimise patient survival. Data evaluating at which time point follow-up has the highest chance to detect recurrence will be most valuable for clinical practice. Novel prognostic markers at surgery should be investigated to determine the risk of relapse over time.

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10. CONFLICT OF INTEREST

All members of the Renal Cell Cancer Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/renal-cell-carcinoma/?type=panel/.

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Renal Transplantation Guidelines aim to provide a comprehensive overview of the medical and technical aspects relating to renal transplantation. It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Renal Transplantation Guidelines panel consists of an international multidisciplinary group of urological surgeons, a nephrologist and a pathologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: http://www.uroweb.org/guideline/renal-transplantation/.

1.4 Publication history

The EAU published the first Renal Transplantation Guidelines in 2003 with updates in 2004 and 2009. A comprehensive update of the 2009 document was published in 2017. This 2021 document is a full update of the 2017 Renal Transplantation Guidelines. The next update of the Renal Transplantation Guidelines will be published in 2023.

2. METHODS

2.1 Introduction

For the 2021 Renal Transplantation Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. Broad and comprehensive literature searches, covering the Renal Transplantation Guidelines were performed, covering a time frame between May 31st 2018 and 1st April 2020. A total of 1,202 unique records were identified, retrieved and screened for relevance. Databases searched included Medline, EMBASE, and the Cochrane Libraries. Detailed search strategies are available online: http://www.uroweb.org/guideline/renal-transplantation/.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review and future goals

This document was subject to independent peer review prior to publication in 2017. Publications ensuing from systematic reviews have all been peer reviewed.

The results of ongoing systematic reviews will be included in the 2022 update of the Renal Transplantation Guidelines. Ongoing systematic reviews include:

1. What is the best treatment for symptomatic obstructive benign prostatic enlargement in renal transplantation patients [5]?
2. For patients with kidney graft stones, does surgical treatment provide better stone free rates than external shock wave lithotripsy [6]?

3. THE GUIDELINE

3.1 Organ retrieval and transplantation surgery

*3.1.1 **Living-donor nephrectomy***

The endoscopic (laparoscopic) approach is the preferred technique for living-donor nephrectomy in established kidney transplant programmes [7]. Nevertheless, open surgery, preferably by a mini-incision approach, can still be considered a valid option, despite increased pain in the post-operative period [8].

Endoscopic living-donor nephrectomy (ELDN) includes:

- Pure or hand-assisted transperitoneal laparoscopy;
- Pure or hand-assisted retroperitoneal approach;
- Laparo-Endoscopic Single Site Surgery (LESS);
- Natural Orifice Transluminal Endoscopic Surgery-assisted (NOTES);
- Laparo-Endoscopic Single Site Surgery and robotic-assisted transperitoneal or retroperitoneal approach.

There is strong evidence in support of laparoscopic living-donor nephrectomy (LLDN), including several systematic reviews and meta-analysis, which have compared its safety and efficacy to open donor nephrectomy. Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival. However, measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures [9-12].

Standard LLDN is usually done through 5 and 12 mm ports, but has also been done with 3 or 3.5 mm ports [13]. According to a recent meta-analysis, hand-assisted LLDN is associated with shorter operative time and warm ischaemia, but equivalent safety and overall results [14]. Laparoscopic living-donor nephrectomy can also be performed with robotic assistance, with equivalent results according to a systematic review [15]. However, the numbers are still low and recent studies, including a meta-analysis, have reported higher complication rates for this approach [16, 17].

Laparo-endoscopic single site surgery nephrectomy allows the surgeon to work through a single incision (usually the umbilicus) with a multi-entry port. The same or a separate incision is then used for kidney withdrawal. Several retrospective and at least three prospective randomised trials demonstrated equivalent safety and results, with a trend towards less pain and better cosmetic results [18, 19]. However, LESS is considered a more technically demanding procedure when compared with classic LLDN and its role is yet to be defined.

Natural orifice transluminal endoscopic surgery-assisted transvaginal nephrectomy avoids the abdominal incision needed for kidney extraction, aimed at minimising scaring and pain. Initial reports suggest that this approach is safe, however experience with this technique is still highly limited [20].

Right LLDN has been considered more difficult, yielding inferior results. However, both left and right LLDN can be performed with equivalent safety and efficacy according to large retrospective studies, systematic reviews and meta-analysis [21, 22].

Laparoscopic living-donor nephrectomy has brought attention to potential failures of different devices such as, endoscopic staplers and locking and non-locking clips, used to secure the renal hilum [21]. There is no scientific evidence that one device is safer than another for securing the renal artery [23-25]. However, the U.S. Food and Drug Administration (FDA) and the manufacturers of locking clips have issued a contraindication against their use in securing the artery during LLDN.

Summary of evidence	LE
Laparoscopic living-donor nephrectomy is associated with similar rates of graft function and rejection, urological complications and patient and graft survival to open nephrectomy.	1a
Measures related to analgesic requirements, pain, hospital stay, and time to return to work are significantly better for laparoscopic procedures.	1a

Recommendations	Strength rating
Offer pure or hand-assisted laparoscopic/retroperitoneoscopic surgery as the preferential technique for living-donor nephrectomy.	Strong
Perform open living-donor nephrectomy in centres where endoscopic techniques are not implemented.	Strong
Perform laparo-endoscopic single site surgery, robotic and natural orifice transluminal endoscopic surgery-assisted living-donor nephrectomy in highly-specialised centres only.	Strong

*3.1.2 **Organ preservation***

In kidneys donated after cardiac death (DCD) evidence suggests that warm ischemia contributes to worse graft outcome. Donor haemodynamic parameters (systolic blood pressure, oxygen saturation and shock index: heart rate divided by systolic blood pressure) may be predictors of delayed graft function (DGF) and graft failure; however, further studies are required to validate this [26]. The duration of asystolic warm ischaemia during procurement in DCD donors is associated with increased risk of graft failure. Overall five year graft failure (including primary graft non-function) was associated with longer asystolic warm ischaemia times [27]. Extraction time (beginning with aortic cross-clamp and ending with placement of the kidneys on ice), is an important factor for DGF. Incidents of DGF were 27.8% and 60% at up to 60 minutes and 120 minutes extraction time, respectively [28].

A retrospective study of 64,024 living donor kidney transplants found that cold ischaemia time (CIT), human leukocyte antigen (HLA) mismatch, donor age, panel reactive antibody, recipient diabetes, donor and recipient body mass index (BMI), recipient race and gender, right nephrectomy, open nephrectomy, dialysis status, ABO incompatibility, and previous transplants were independent predictors of DGF in living donor kidney transplants [29]. Five-year graft survival among living donor kidney transplant recipients with DGF was significantly lower than in those without DGF. Delayed graft function increased the risk of graft failure by more than two-fold [29].

3.1.2.1 Kidney storage solutions and cold storage

There are two main sources for kidney graft injury: ischaemia (warm and cold), and reperfusion injury. The aims of modern kidney storage solutions include: control of cell-swelling during hypothermic ischaemia; maintenance of intra- and extra-cellular electrolyte gradient during ischaemia; buffering of acidosis; provision of energy reserve; and minimisation of oxidative reperfusion injury. There is no agreement on which of the mechanisms is most important for post-ischaemic renal graft function [30]. No storage solution seems to combine all mechanisms. Previously, Euro-Collins was widely used, but is no longer recommended.

Presently, University of Wisconsin (UW), and histidine-tryptophan-ketoglutarate (HTK) solution are equally effective and are standard for multi-organ or single kidney harvesting procedures. The characteristics of HTK are its low viscosity, low potassium concentration and low cost. University of Wisconsin solution has been the standard static cold preservation solution for the procurement of liver, kidney, pancreas, and intestine [31]. University of Wisconsin, HTK, and Celsior solutions have provided similar allograft outcomes in most clinical trials; however, some differences have become apparent in recent studies and registry reports [32, 33]. Marshall's hypertonic citrate solution (MHCS) is also suitable for use in the preservation of human kidneys before transplantation [34]. In experimental studies of kidney preservation, HTK and UW retained a greater capacity to preserve endothelial structure and pH buffering function during warm ischaemia in comparison to MHCS and Celsior, especially in uncontrolled DCD donors [35]. In the absence of a cost-utility analysis, the results of the meta-analysis from the randomised controlled trials (RCTs) comparing UW with Celsior and MHSC in standard cadaver donors, indicate that these cold storage solutions are equivalent [36].

For living donors, in whom immediate kidney transplantation is planned, perfusion with crystalloid solution is sufficient. Kidneys coming from DCD donors, especially those uncontrolled, are high-risk marginal organs due to prolonged warm ischaemia periods, and require specific measures in order to diminish the rate of non-function or DGF. More than 60% of kidney grafts currently come from Expanded Criteria Donors (ECD) (any donor aged > 65 years and/or donor aged > 55 years with any of the following: acute renal dysfunction, stroke or arterial hypertension) [37].

Summary of evidence	**LE**
University of Wisconsin and HTK solution are equally effective and are standard for multi-organ or single kidney harvesting procedures.	1b
A meta-analysis of RCTs indicated that UW and Celsior solution are equivalent in standard cadaver donors.	1a

Recommendations	**Strength rating**
Use either University of Wisconsin or histidine tryptophane ketoglutarate preservation solutions for cold storage.	Strong
Use Celsior or Marshall's solution for cold storage if University of Wisconsin or histidine tryptophane ketoglutarate solutions are not available.	Strong

3.1.2.2 Duration of organ preservation

Cold ischaemia time should be as short as possible. Kidneys from ECDs after brain death (DBD) and DCD donors are more sensitive to ischaemia than standard criteria donors. Kidneys from DBD donors should ideally be transplanted within a 18 to 21 hour time period; there is no significant influence on graft survival within a 18 hour CIT [36, 38, 39]. Kidneys from DCD donors should ideally be transplanted within 12 hours [40], whilst kidneys from ECDs should ideally be transplanted within 12 to 15 hours [41, 42].

3.1.2.3 Methods of kidney preservation: static and dynamic preservation

Whichever method is used, cold storage is critical. The use of cold preservation as a therapeutic window to deliver pharmacological or gene therapy treatments could, from an investigational point of view, improve both short- and long-term graft outcomes [43]. Cooling reduces the metabolic rate of biological tissue minimising continuous cellular processes that lead to depletion of ATP and accumulation of metabolic products. Reperfusion with oxygenated blood invokes ischaemia-reperfusion injury. Hypothermic perfusion does not enable normal cellular metabolic function or prevent depletion of energy stores [44]; however, it prevents the deleterious effects of simple cooling, especially in the setting of prolonged warm-ischaemic time in uncontrolled DCD donors. Two meta-analyses suggest that hypothermic machine perfusion (HMP) reduces DGF compared with static cold storage [45, 46]. Outcomes for primary non-function (PNF) are less clear, but one meta-analysis limited to high quality studies suggests a reduction in PNF rates with HMP [46]. A Cochrane systematic review and meta-analysis showed that HMP reduced the risk of DGF when compared to static cold storage (CS) for kidneys from both DCD and DBD donors [47].

The increased demand for organs has led to the increased use of "higher risk" kidney grafts. Kidneys from DCD donors or grafts coming from ECDs are more susceptible to preservation injury and have a higher risk of unfavourable outcomes [48, 49].

Dynamic, instead of static, preservation could allow for organ optimisation, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve vulnerable grafts. Preclinical findings have driven clinical organ preservation research that investigates dynamic preservation, in various modes (continuous, pre-implantation) and temperatures (hypo-, sub-, or normothermic) [44].

There are several methods of kidney preservation including:

- Initial flushing with cold preservation solution followed by ice storage. However, the limitations of static CS in preserving marginal organs such as ECD kidneys has led to the increased use of dynamic methods.
- Current dynamic preservation strategies entering clinical practice and the different modalities of their use are: HMP, hypothermic regional perfusion, normothermic machine perfusion, normothermic regional perfusion, sub-normothermic machine perfusion and sub-normothermic regional perfusion [44].
- Continuous pulsatile HMP seems to be a good preservation method for marginal organs, either initially or after a period of simple CS (shipping of suboptimal kidneys) [50].

- Some evidence shows that hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury. The perfusion solutions used are specific, and are qualitatively different to CS solutions [33].
- Nonoxygenated HMP of the kidney at low perfusion pressures (20-30 mmHg) has been shown to reduce DGF [45]. The largest RCT comparing simple CS with HMP of deceased donor kidneys showed an overall reduced risk of DGF and a survival benefit, most pronounced in ECD kidneys [51]. Hypothermic machine perfusion of kidneys from type III DCD donors decreased DGF with no impact on graft survival [48].
- Hypothermic machine-perfusion reduces the risk of DGF in standard criteria DBD donor kidneys regardless of CIT [52].
- Increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF; however, they do not justify discarding the kidney. The flow perfusion value seems to be an indicator of graft viability in uncontrolled DCD donors, particularly donors with a high creatinine level [53]. However, research is required to identify a strong and reliable measure for predicting kidney viability from machine perfusion [36]. Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts [54].
- The effect of oxygenated HMP was investigated in an RCT initiated by the Consortium on Organ Preservation in Europe on type III DCD kidneys and ECD kidneys [44]. Graft loss was significantly lower after oxygenated HMP compared to HMP [55]. No significant differences between the two groups were shown for DGF, PNF and patient death. No difference in eGFR at one year was observed between HMPO vs. HMP; however, sensitivity analysis, accounting for all-cause graft failure, showed a higher eGFR in oxygenated HMP [55].
- A short period of normothermic machine perfusion (NMP) immediately prior to implantation has been shown to improve kidney graft function, replenish ATP and reduce injury in experimental models [56, 57].
- A retrospective study of normothermic regional perfusion (NRP) in uncontrolled DCD donors concluded that NRP appears to decrease graft failure when used as a preconditioning technique with subsequent HMP preservation in these donors [58].
- Active research is being developed on preservation of prolonged warm-ischaemically damaged human kidneys (types I and II DCD) by *in situ* normothermic extracorporal hemoperfusion with oxygenation and leukocyte depletion before procurement [59]. Oxygen carriage is achieved by using blood depleted of leukocytes. Potential advantages of this preservation technique are reduction in ischaemia-reperfusion injury as well as the possibility of assessing organ viability.
- Currently there is one registered ongoing RCT on pre-implantation NMP using an oxygenated, sanguineous normothermic perfusion solution (http://www.isrctn.com/ISRCTN15821205). However, kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output [60].
- Continuous subnormothermic machine perfusion and controlled oxygenated rewarming has demonstrated improved creatinine clearance and preservation of structural integrity compared with continuous oxygenated HMP in a research setting [61].

Summary of evidence	**LE**
A meta-analysis of RCTs comparing CS with HMP of deceased donor kidneys showed a reduced risk of DGF for HMP.	1a
Hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury.	2a
Perfusion parameters (renal flow and renal vascular resistance) have low predictive values and should not be used as the sole criterion to assess viability of kidney grafts.	2b

Recommendations	**Strength rating**
Minimise ischaemia times.	Strong
Use hypothermic machine-perfusion (where available) in deceased donor kidneys to reduce delayed graft function.	Strong
Hypothermic machine-perfusion may be used in standard criteria deceased donor kidneys.	Strong
Use low pressure values in hypothermic machine perfusion preservation.	Strong
Hypothermic machine-perfusion must be continuous and controlled by pressure and not flow.	Strong
Do not discard grafts based only on increased vascular resistance and high perfusate injury marker concentrations during hypothermic machine perfusion preservation.	Weak

3.1.3 ***Donor Kidney biopsies***

Donor kidney biopsies can serve different purposes including:

- histological assessment of organ quality prior to transplantation (often referred to as procurement or harvest biopsies);
- histological analysis of focal lesions, especially if there is a suspicion of neoplasia;
- detection of donor derived lesions as reference for subsequent post-transplant biopsies (often referred to as baseline, zero-time or implantation biopsies).

3.1.3.1 Procurement Biopsies

3.1.3.1.1 Background and prognostic value

Procurement biopsies are used for the detection of tissue injury to aid the decision of whether or not a deceased donor kidney is suitable for transplantation. These biopsies are most commonly performed in donors with clinical suspicion of chronic kidney injury (ECDs) [62].

Kidney discard in Europe is rarely based on histology findings, as procurement biopsies are not regularly performed for graft allocation in the Eurotransplant region [62]. However, since biopsy findings are the most frequent cause for discarding donor organs in the United States [63-65], their prognostic value has been analysed in numerous studies. A recently published systematic review of studies on donor kidney biopsies revealed a lack of prospective studies and marked heterogeneity regarding the type of lesions being assessed, their scoring, the definitions of post-transplant outcomes and the statistical methods employed [66]. Therefore, the published evidence suggests that the use of procurement biopsies for deciding on suitability for transplantation of donor kidneys may have some important limitations including the following [62, 66, 67]:

- *There is no consistent association between histological lesions observed in donor kidney biopsies and post-transplant outcomes.*

The concept of procurement biopsies in elderly donors was introduced by a study from Gaber *et al*., in 1995. This study observed significantly worse outcomes in recipients of kidneys with > 20% globally sclerotic glomeruli [68]. However, subsequent studies yielded highly variable results and it cannot be concluded that glomerulosclerosis is independently associated with graft outcomes [66]. A similar variability was also observed for other potentially relevant lesions like arterial injury, interstitial fibrosis and tubular atrophy with each showing predictive value in some studies, but not in others [66].

- *There is no agreement on prognostically relevant lesions and how they should be scored.*

Specific grading systems for donor kidney biopsies have not yet been developed. Lesion scoring in pre-transplant biopsies is mostly based on the Banff consensus for post-transplant renal allograft pathology, which is supported by the 2007 Banff Conference report [69].

Many attempts have been made to use composite semi-quantitative scoring systems to express the global extent of tissue injury in donor kidney biopsies. These scoring systems are mostly based on simple addition of the Banff scores for individual lesions, most commonly glomerulosclerosis, arteriolar hyalinosis, arterial intimal fibrosis, interstitial fibrosis and tubular atrophy and rarely include clinical parameters like donor age [70], serum creatinine values and donor hypertension [71].

A limited number of histological scoring systems are based on modelling analysis [70-74]. Only the Maryland Aggregate Pathology Index (MAPI) [74] scoring system and the Leuven donor risk score [70], use graft failure as their endpoint and have been independently validated in a second cohort. Other studies used surrogate clinical endpoints like DGF [72] and estimated glomerular filtration rate (eGFR) at three months [73] to calculate histological models. In addition, these models were not validated in independent cohorts. The variation in how the components are weighted to achieve the composite score and the different endpoints used may explain the conflicting conclusions in the literature [62, 66, 67].

- *Due to the time constraints of organ allocation procurement biopsies are mostly read on frozen sections by on-call pathologists, which might affect the diagnostic reliability of reported findings.*

This may have substantial impact on the diagnostic reliability of the procedure since frozen sections are prone to morphological artefacts that can impair the detection and scoring of potentially important lesions such as arteriolar hyalinosis and interstitial fibrosis [75, 76]. There is strong evidence that dedicated renal pathologists should examine formalin-fixed paraffin-embedded core-needle biopsies. Paraffin histology employing special stains is technically superior to frozen sections since morphological details are better preserved on paraffin sections than on frozen sections and potentially confounding artefacts can be avoided. Rapid processing of tissue for paraffin histology is technically feasible, but the respective protocols are not universally implemented and are not available on a 24/7 basis in most departments. Another source of variability is the professional experience of the pathologist in charge. Procurement biopsies are commonly read by the on-call general

pathologist who frequently has no specific training in renal pathology. A recent study specifically addressing this issue found that the on-call pathologists tended to overestimate chronic injury in biopsies [77].

3.1.3.2 Type and size of biopsy

Many transplant centres obtain wedge biopsies of donor kidneys rather than needle biopsies due to the presumed higher risk of bleeding complications with the latter. Wedge biopsies sample the cortex superficially whereas needle biopsies reach deeper aspects of the cortex. Needle biopsies also allow sampling from different areas of the kidney. Submit 14 or 16 G needle biopsies as obtaining adequate biopsies with 18 G needles requires multiple cores [78]. Several studies comparing wedge with needle biopsies concluded that needle biopsies perform much better in the evaluation of vascular lesions because interlobular arteries are rarely sampled in wedge biopsies. Both methods were comparable for glomerular or tubulointerstitial lesions [79-82]. It was also demonstrated that glomerulosclerosis is significantly more pronounced in the subcapsular zone compared with deeper areas of the cortex [83]. The problem of insufficient sampling of arteries and over representation of (subcapsular) glomerular scars in wedge biopsies, can only be avoided if particular attention is paid to the correct performance of the biopsy, with a minimal depth of 5 mm [84]. The predictive value of glomerulosclerosis increases significantly with higher numbers of glomeruli in the wedge biopsy, with ideally at least 25 glomeruli required for evaluation [81]. There is limited evidence regarding complication rates in pre-implantation biopsies.

Use of a skin punch biopsy device might be an attractive alternative. Skin punch biopsies measure 3 mm in diameter. They have a shorter length than needle biopsies therefore avoiding injury to large calibre arteries at the corticomedullary junction whilst still sampling tissue from deeper areas of the cortex [85].

3.1.3.3 Summary of evidence and recommendations

Summary of evidence	**LE**
Individual histologic lesions like glomerulosclerosis, arterial luminal narrowing or tubulointerstitial injury observed in donor kidney biopsies have limited prognostic value for long-term allograft survival.	3
Composite histological scoring systems provide a more comprehensive measure of overall organ damage. However, published scoring systems still lack independent validation and robust thresholds.	3
Size of the biopsy is of critical importance for its diagnostic value. An adequate biopsy reaches beyond the immediate subcapsular area (≥ 5 mm) and contains ≥ 25 glomeruli and ≥ one artery. Needle biopsies, wedge biopsies or specimens obtained with a skin punch biopsy device will result in equally adequate biopsies if sampling is properly performed. Obtaining adequate biopsies with 18 G needles is difficult and requires multiple cores.	3

Recommendations	**Strength rating**
Do not base decisions on the acceptance of a donor organ on histological findings alone, since this might lead to an unnecessary high rate of discarded grafts. Interpret histology in context with clinical parameters of donor and recipient including perfusion parameters where available.	Strong
Use paraffin histology for histomorphology as it is superior to frozen sections; however, its diagnostic value has to be balanced against a potential delay of transplantation.	Strong
Procurement biopsies should be read by a renal pathologist or a general pathologist with specific training in kidney pathology.	Strong

3.1.3.4 Implantation biopsies

Implantation biopsies are used to provide baseline information on donor kidney injury for comparison with subsequent post-transplant kidney biopsies. Baseline biopsies can be essential for clear distinction between pre-existing damage and acquired lesions. They are particularly valuable in cases of thrombotic microangiopathy, arteriolar hyalinosis or acute tubular injury. In contrast to procurement biopsies that are obtained at the time of organ harvesting, implantation biopsies are usually taken before implantation in order to cover potential effects of CIT. Their diagnostic contribution has not been formally quantified in the literature which might be due to the difficulties of measuring the value of implantation biopsies for improving diagnoses. Despite the lack of formal studies investigating their value it seems very reasonable to perform implantation biopsies in deceased donor kidneys.

*3.1.4 **Living and deceased donor implantation surgery***

3.1.4.1 Anaesthetic and peri-operative aspects

Good communication between nephrologists, anaesthetists and surgeons is required for optimal anaesthetic and peri-operative care of the renal transplant patient. Anaesthetic care of the living kidney donor [86] and renal transplant recipient [87] have been reviewed and recent guidelines from the European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA) [88] are cross referenced.

3.1.4.2 Immediate pre-op haemodialysis

Routine use of haemodialysis immediately prior to renal transplantation is not indicated [88]. Hyperkalaemia is the most common indication for haemodialysis pre-operatively. The risks of haemodialysis compared with medical therapy must be considered along with the risks of intra-operative fluid overload, electrolyte and acid-base disturbances, particularly where a deceased donor kidney is transplanted with a significant risk of DGF. Pre-operative haemodialysis may initiate a pro-inflammatory state, delay surgery, increase the CIT and increase the risk of DGF [89].

Summary of evidence	**LE**
Pre-operative haemodialysis has the potential to delay transplantation, increase CIT and increase the risk of DGF.	2

Recommendation	**Strength rating**
Use dialysis or conservative measures to manage fluid and electrolyte imbalance prior to transplant surgery taking into consideration the likelihood of immediate graft function.	Weak

3.1.4.3 Operating on patients taking anti-platelet and anti-coagulation agents

Many patients active on the transplant waiting list have vascular disease and/or a pro-thrombotic condition that should be risk-assessed prior to transplantation. Dual anti-platelet therapy is commonly given to patients with coronary artery stents for six to twelve months; peri-operative management plans for these patients should be discussed with a cardiologist so that the risks of withdrawal of the anti-platelet agent can be fully considered. Options for reversal of anti-coagulation and post-operative anti-coagulation should be discussed with a haematologist prior to patient listing.

Some patients will be active on a transplant waiting list whilst continuing to take anti-platelet and/or anti-coagulation agents. The indication for anti-platelet or anti-coagulation agents should be clearly documented for each individual. Potential increased risk of peri-operative bleeding needs to be weighed against potential harm from arterial or venous thrombosis. In accordance with the American College of Chest Physicians and the European Society of Cardiology guidelines [90, 91], the literature suggests that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications [92], however, the number of patients studied was low. If needed, the effect of anti-platelet agents can be reduced with intra-operative platelet infusions.

Summary of evidence	**LE**
A retrospective single-centre case-control study in patients undergoing kidney transplantation concluded that continuing anti-platelet therapy with aspirin, ticlopidine or clopidogrel does not confer a significantly greater risk of peri/post-operative complications.	3

Recommendations	**Strength rating**
Consider continuing anti-platelet therapy in patients on the transplant waiting list.	Weak
Discuss patients who take anti-platelet and anti-coagulation agents prior to transplant surgery with relevant cardiologist/haematologist/nephrologist.	Weak

3.1.4.4 What measures should be taken to prevent venous thrombosis including deep vein thrombosis during and after renal transplant?

Peri-operative administration of short-acting anti-coagulation agents reduces peri-operative risk of venous thrombosis (including in ileo-femoral and renal veins); however, due to associated increased blood loss administration requires knowledge of individual patient risk factors. None of the current major thrombosis prevention guidelines directly address thromboprophylaxis in the renal transplant peri-operative period. A small

RCT [93] showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation. Those administered prophylactic anti-coagulation had significantly lower haemoglobin whilst those administered prophylactic unfractionated heparin had prolonged lymph drainage. Based on this study, routine pharmacological prophylaxis is not recommended in low-risk living donor recipients. Mechanical measures to decrease ileo-femoral deep vein thrombosis (DVT) can be used where there is no contraindication due to peripheral vascular disease particularly where there are concerns about bleeding risks with pharmacological prophylaxis.

Summary of evidence	**LE**
A small RCT (n=75) showed no difference in early post-operative graft loss or thromboembolic complications with or without prophylactic anti-coagulation.	1b

Recommendation	**Strength rating**
Do not routinely give post-operative prophylactic unfractionated or low-molecular-weight heparin to low-risk living donor transplant recipients.	Weak

3.1.4.5 Is there a role for peri-operative antibiotics in renal transplantation?

Prophylactic peri-operative antibiotics are generally used in renal transplant surgery but the optimal antibiotic regimen is not known and increasing antibiotic resistance may hamper their effectiveness in this setting. A multicentre, prospective RCT showed no difference at one month in surgical site, bacterial, fungal or viral infection between those receiving a single dose broad spectrum antibiotic at induction of anaesthesia compared to those receiving antibiotic 12 hourly for 3-5 days [94]. A retrospective comparison of peri-operative intravenous cefazolin prophylaxis compared to no antibiotic showed no difference in infectious complications (surgical site, urinary tract, bacteraemia or central catheter-related infection) in the first month after renal transplantation [95].

Summary of evidence	**LE**
A multicentre, prospective RCT showed that the incidents of surgical site infection and urinary tract infection were similar in those receiving a single dose broad spectrum antibiotic at induction of anaesthesia and those receiving antibiotics 12 hourly for 3-5 days.	1b

Recommendation	**Strength rating**
Use single-dose, rather than multi-dose, peri-operative prophylactic antibiotics in routine renal transplant recipients.	Strong

3.1.4.6 Is there a role for specific fluid regimes during renal transplantation and central venous pressure measurement in kidney transplant recipients?

Careful peri- and post-operative fluid balance is essential for optimal renal graft function. There is no evidence determining if crystalloids or colloids are better for intravenous fluid management during renal transplant surgery, however colloids may be immunogenic. If normal saline (0.9%) is used, monitoring for metabolic acidosis is recommended in the peri-operative period. A prospective double-blind RCT compared normal saline to lactated Ringer's solution as intra-operative intravenous fluid therapy. Serum creatinine at day three post-surgery did not differ between the two groups. However, Ringer's lactate caused less hyperkalaemia and metabolic acidosis than normal saline. Balanced solutions may be the optimal and safer option for intra-operative intravenous fluid therapy [96].

Central venous pressure (CVP) measurement helps anaesthetists guide fluid management. A small prospective non-blinded RCT compared two normal (0.9%) saline regimens: constant infusion (10-12 $mL/kg^{-1}/h^{-1}$ from start of surgery until reperfusion) and CVP-based infusion (target CVP appropriate to stage of operation) [97]. Central venous pressure directed infusion produced a more stable haemodynamic profile, better diuresis and early graft function. Directed hydration may decrease DGF rates and CVP measurement may help optimise early graft function.

Summary of evidence	LE
A small (n=51) prospective RCT found that use of Ringer's lactate solution was associated with less hyperkalaemia and acidosis compared with normal saline in patients undergoing kidney transplantation.	1b
A small (n=40) prospective RCT comparing constant infusion vs. CVP found that CVP produced a more stable haemodynamic profile, better diuresis and early graft function.	1b

Recommendations	Strength rating
Optimise pre-, peri- and post-operative hydration to improve renal graft function.	Strong
Use balanced crystalloid solutions for intra-operative intravenous fluid therapy.	Weak
Use target directed intra-operative hydration to decrease delayed graft function rates and optimise early graft function.	Strong

3.1.4.7 Is there a role for dopaminergic drugs, furosemide or mannitol in renal transplantation?

Low-dose dopamine (LDD) has been used in renal transplantation due to a perceived improvement in urine output and early graft function. Use of LDD in kidney donors is outside of the scope of this section. Conflicting results prevent a consensus statement on routine use of LDD in transplant recipients. A small (n=20) prospective randomised cross-over study in deceased donor renal transplantation suggested significant improvements in urine output and creatinine clearance in the first nine hours post-surgery without adverse events [98]. By contrast, a retrospective comparison of LDD in the first twelve hours post-deceased donor renal transplantation showed no difference in diuresis or kidney function, but those administered LDD (n=57) had increased heart rates, longer intensive therapy unit stay and higher six-month mortality than those not treated with LDD (n=48) [99].

Considerable variation exists in the use of diuretics during renal transplant recipient surgery and there is little evidence to suggest any benefit from their use [100]. No evidence on the use of mannitol during renal transplant recipient surgery was found during the panel's literature search. Use of mannitol in kidney donors is outside the scope of this section.

Summary of evidence	LE
A retrospective comparative study of LDD treated vs. non-treated renal transplantation patients concluded that LDD administration did not improve kidney function in the first twelve hours post renal transplantation, but did result in increased heart rates, longer intensive therapy unit stay and higher six-month mortality in those receiving LDD.	2b

Recommendation	Strength rating
Do not routinely use low-dose dopaminergic agents in the early post-operative period.	Weak

3.1.5 ***Surgical approaches for first, second, third and further transplants***

Transplant (bench/back-table) preparation is a crucial step in the transplantation process. The kidney must be inspected whilst on a sterile ice slush, removing peri-nephric fat when possible to permit inspection of the quality of the organ and to exclude exophytic renal tumours. Biopsy of the kidney on the back-table may be performed to help in the multifactorial decision-making process regarding the quality and usage of the kidney for both single and/or dual transplantation. Suspicious parenchymal lesions also require biopsy. Techniques for intra-operative kidney biopsy are discussed in section 3.1.3.

The number, quality and integrity of renal vessels and ureter(s) should be established and lymphatics at the renal hilum ligated. The quality of the intima of the donor renal artery should be evaluated. Branches of the renal artery not going to the kidney or ureter(s) should be tied.

In deceased donor kidney transplantation the quality of the aortic patch should be determined. If severe atheroma of the patch, ostium or distal renal artery is seen then the aortic patch and/or distal renal artery can be removed to provide a better quality donor renal artery for implantation. Back table reconstruction of multiple donor arteries is discussed in section 3.1.5.1. The length of the renal vein should be evaluated. Renal vein branches should be secured/tied.

For a deceased donor right kidney, lengthening the renal vein on the back table may be performed if needed with donor inferior vena cava (IVC) [101]. Techniques for lengthening a short living donor right renal vein from donor gonadal vein or recipient saphenous vein require pre-operative planning and specific consent (discussed in section 3.1.5.1).

The length, quality and number of the ureter(s) should be established. The peri-pelvic and proximal peri-ureteral tissue in the 'golden triangle' should be preserved.

Recommendation	Strength rating
Assess the utility (including inspection) of the kidney for transplantation before commencement of immunosuppression and induction of anaesthesia for deceased donor kidney transplantation.	Strong

3.1.5.1 Single kidney transplant - living and deceased donors

The standard surgical approach for first or second single kidney transplant (SKT) operations remains open kidney transplant (OKT). Emerging surgical technologies using minimal access surgical approaches have been developed and the different surgical approaches (minimally invasive open, laparoscopic and robot-assisted) were compared in a systematic review [102].

An extra-peritoneal approach to either iliac fossa should be used as the operative approach in most first or second SKT operations. There is no evidence to prefer placement of a left or right kidney into either iliac fossa [103]. Peri-iliac vessel lymphatics should be ligated to try and prevent post-operative lymphocele. Appropriate segments of iliac artery and vein should be mobilised to facilitate appropriate tension-free vascular anastomoses and the final positioning of the transplanted kidney. There is evidence supporting the benefits of cooling the kidney surface during implantation [104].

Recommendations	Strength rating
Choose either iliac fossa for placement of a first or second single kidney transplant.	Weak
Ligate peri-iliac vessel lymphatics (lymphostasis) to reduce post-operative lymphocele.	Weak

A variety of techniques have been described to help with the anastomosis of a short renal vein. This is most commonly encountered with a right kidney, especially from a living donor. To achieve equivalent outcomes with right kidneys appropriate surgical technical manoeuvres may be needed to optimise right kidney implantation.

A number of studies suggest marginally worse outcomes with use of the right compared to left kidney. two large registry studies demonstrate a slightly higher risk of early graft failure using right compared to left kidneys from living donors [105-107]. A registry study of 2,450 paired kidneys, donated after cardiac death, observed with right kidneys: more early surgical complications; an increased risk in DGF (Odds Ratio [OD] 1.46); and inferior one year graft survival (OD 1.62), but not at subsequent time points [105]. However, surgical techniques used to compensate for a right kidney, anastomosis time and surgeon experience were not recorded. A recent registry study of 87,112 deceased-donor kidney recipient pairs reported a modest increase in DGF (adjusted OD 1.15) and all-cause graft failure (adjusted hazard ratio 1.07), within the first six months, associated with use of the right kidney, but there was no association with recipient mortality [108]. Furthermore, data from cohort studies [101, 103] and one registry study [104] suggest equivalent outcomes with either left or right deceased donor kidneys. Meta-analysis of data from one RCT and fourteen cohort studies suggested equivalent graft outcomes [109]. Overall, these findings do not support declining an organ for kidney transplantation based on laterality of kidney offered.

Techniques to manage a short renal vein can be addressed in the donor and/or recipient. Ligation of internal iliac vein(s) may be necessary to elevate the iliac vein and avoid tension on the renal vein anastomosis [103]. Transposition of the iliac artery and vein may enhance the position for the venous anastomosis [110]. The right renal vein may be lengthened. With deceased donor kidneys this is usually done with donor IVC [111]. In living donors, lengthening of the renal vein may be achieved with donor gonadal vein retrieved at donor nephrectomy [112] or with recipient saphenous vein [113], although both require specific consent and in general the other aforementioned techniques are preferred.

Summary of evidence	LE
Prospective cohort studies demonstrated that: • transposition of the recipient iliac vein is an appropriate technical solution to compensate for the short length of the renal vein in right kidney LDN (n=43); • the living donor right kidney renal vein can be successfully lengthened using donor gonadal vein (n=17) or recipient saphenous vein (n=19).	3

Recommendation	Strength rating
Assess the length of the donor renal vein and if it is short consider one of a variety of surgical techniques to optimise the venous anastomosis.	Weak

A history suggesting previous iliac or femoral vein thrombosis should initiate pre-operative imaging to establish patency of one iliac vein and the IVC. An intra-operative finding of an unexpected iliac vein and/or vena cava thrombosis may lead to abandonment of implantation. With pre-operative planning, native renal (orthotopic) or superior mesenteric vein or gonadal vein collaterals can be used.

The external or common iliac arteries are equally good for arterial anastomosis. The internal iliac artery is more frequently affected by atherosclerosis than the external or common iliac arteries. End-to-side anastomosis of donor renal artery to recipient external and/or common iliac artery is recommended in general over an end-to-end anastomosis to the internal iliac artery. The only RCT comparing these techniques suggests no difference [114]; however, the study was limited by small numbers and a high (8%) overall renal artery thrombosis rate.

The sites of the vascular anastomosis should be chosen carefully according to the length of the renal artery and vein to avoid kinking of the vessels when the kidney is placed into its final location, usually in the iliac fossa. The site of the arterial anastomosis should avoid atheromatous plaques in the iliac artery to decrease the risk of iliac artery dissection. The intima of the donor and recipient arteries should be checked prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to, or as part of, the arterial anastomosis.

A Carrel patch is usually maintained on a deceased donor renal artery although it can be removed if there is either severe ostial atheroma/stenosis (with good quality proximal renal artery) or if the length of the renal artery is too long for the appropriate implantation site on the iliac artery (which is more common with the right renal artery).

Multiple renal arteries supplying a deceased donor kidney can be maintained on a Carrel patch (of appropriate length) and implanted as a single anastomosis. In living donor transplantation, multiple renal arteries require a variety of strategies to achieve optimum re-perfusion [100]. Two arteries can be implanted separately or to achieve a single anastomosis: a very small second artery (especially if supplying the upper pole) may be sacrificed; the two arteries may be joined together (as a trouser graft); or the smaller artery can be anastomosed onto the side of the main artery (end-to-side anastomoses). A lower polar artery may be re-vascularised via anastomosis to the inferior epigastric artery [115]. In living donor transplantation where three or more donor arteries exist, consideration should be given to alternate kidney donors. In circumstances using a living donor kidney with three or more donor arteries, strategies include a combination of the above techniques or, after appropriate consent, use an explanted (recipient's own) internal iliac artery graft [116] or saphenous vein graft [117].

In cases where an iliac artery prosthetic replacement has previously been carried out because of severe symptomatic iliac atheroma, the renal artery should be implanted into the prosthesis. Administration of systemic heparin should be considered prior to clamping of a vascular prosthesis [118].

A variety of sutures and suturing techniques for the vascular anastomosis are described, but in general practice, a 5/0 and 6/0 non-absorbable mono-filament polypropylene suture(s) are used for the renal vein and renal artery anastomosis. Despite this, there is no evidence to recommend one suturing technique over another to prevent, for example, transplant artery stenosis. Use of an expanded polytetrafluroethylene suture compared to standard polypropylene suture may reduce blood loss due to a better needle/thread ratio [119].

In third or further transplants the surgical approach must be planned pre-operatively so that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney [120, 121]. Nephrectomy of an old transplant kidney may be required prior to transplantation or at the time of transplantation [120]. Mobilisation of the common or internal iliac artery, internal iliac vein or IVC may be required. An intra-peritoneal approach (via the iliac fossa or midline) may be required [122]. Rarely orthotopic transplantation is needed [120, 123].

Evidence suggests that minimising the anastomosis time and/or rewarming time results in reduced DGF [124]. The effect on long term graft function is uncertain, but may also be impacted by short anastomosis time [125].

Summary of evidence	LE
A small RCT (n=38) comparing end-to-end anastomosis to the internal iliac artery vs. end-to-side anastomosis to the external iliac artery found that both techniques showed similar results in the post-operative period and at three-years follow-up.	1b
Cohort studies have demonstrated third or further transplants are a valid therapeutic option with reasonable short- and long-term patient and graft survival.	3

Recommendations	Strength rating
Use the external or common iliac arteries for an end-to-side arterial anastomosis to donor renal artery.	Weak
Use an end-to-end anastomosis to the internal iliac artery as an alternative to external or common iliac arteries.	Weak
Check the intima of the donor and recipient arteries prior to commencing the arterial anastomosis to ensure that there is no intimal rupture/flap. If this is found it must be repaired prior to/as part of the arterial anastomosis.	Strong
Pre-operatively plan the surgical approach in third or further transplants, to ensure that appropriate arterial inflow and venous outflow exists with adequate space to implant the new kidney.	Strong

3.1.5.2 Robot-assisted kidney transplant surgery

Robot-assisted kidney transplant (RAKT) surgery using living donor kidneys has been evaluated in multi-centre prospective non-randomised studies (using IDEAL consortium principles) [126]. Single-centre prospective non-randomised studies are on-going addressing RAKT with use of deceased donor kidneys. Both trans- and extra-peritoneal approaches for RAKT are described. Potential advantages of RAKT may exist (decreased post-operative pain, incision length and lymphocele rate). Potential issues with RAKT are the exclusion of recipients with severe atherosclerosis or third (or further) kidney transplants, a higher than expected rate of DGF and a small number of reported early arterial thromboses despite carefully selected cases [127]. The learning curve for RAKT has been reported to be 35 cases for experienced surgeons in a retrospective multicentre series of 187 patients undergoing RAKT [128]. Complication and DGF rates decreased significantly and plateaued after the first 20 cases. The rate of Clavien-Dindo grade III/IV complications was 14% during the first ten RAKTs, but only 3% after this [128]. The rate of arterial graft thrombosis (1.6%) was comparable with that for open kidney transplant (0.5 - 3.5%) [128]. A ten year single-centre retrospective analysis of 239 obese RAKT patients concluded that RAKT can be safely performed in obese patients with minimal risk of developing a surgical site infection [129]. A graft failure rate of 7.1% was reported during follow-up mostly due to acute rejection. Patient and graft survival was 95% and 93% at three years, respectively [129]. Evidence is too premature to recommend RAKT outside of appropriately mentored prospective studies.

3.1.5.3 Dual kidney transplants

Dual kidney transplant (DKT) is performed when the quality of a single deceased donor kidney is thought to be insufficient for appropriate long-term graft function and that the outcome with both kidneys would be better. A variety of surgical techniques have been described to implant the pair of donor kidneys [130]. These include unilateral extra-peritoneal (UEP) or intra-peritoneal (UIP) and bilateral extra-peritoneal (BEP) or intra-peritoneal (BIP) that can be via a midline [131] or two lateral incisions.

The aim of a unilateral approach is to leave the contralateral iliac fossa intact for future transplantation in the event of graft loss and to reduce CIT for the second kidney transplant [132]. The unilateral approach may require mobilisation and division of the internal iliac vein to facilitate the two renal veins to iliac vein anastomoses. Modifications of the unilateral technique include single renal artery and vein anastomoses (with bench reconstruction) to further reduce CIT for the second kidney [133-135]. Dual kidney transplant takes longer and has higher blood loss than SKT regardless of the technique used. Data suggest shorter operative time and hospital stay with UEP compared to BEP [136], but other data suggest similar outcomes from all DKT techniques. No RCT exists to recommend one technique for all patients or situations.

En-bloc retrieval is performed when kidneys are retrieved from children weighing < 15 kg. Depending on the size of the donor kidney and size and weight of the adult recipient(s), *en-bloc* transplantation of the two kidneys may be performed or, if appropriate, the aorta and IVC patch may be divided for SKT [137].

3.1.5.4 Ureteric implantation in normal urinary tract

Ureteric anastomotic techniques described for renal transplant recipients with no underlying urological abnormality include: extra (Lich-Gregoir) or intra (Leadbetter-Politano) vesical uretero-neo-cystotomy and uretero-ureterostomy using native ureter. A meta-analysis [138] of two RCTs and 24 observational studies

favoured the extra-vesical Lich-Gregoir technique to an intravesical approach leading to reduced overall complications (specifically urine leak, stricture and post-operative haematuria). Fewer urinary tract infections (UTIs) were observed with the extravesical approach when compared with the intra-vesical technique in one RCT [139]. Pyelo- or uretero-ureterostomy to the ipsilateral native ureter has been described as a primary technique in recipients with non-refluxing native ureters [140]. A meta-analysis suggested ureteric stricture, obstruction, and stone formation were more common after uretero-ureterostomy whereas vesicoureteral reflux and UTIs were more common after uretero-neo-cystostomy [141].

The donor ureter should be kept as short as possible with peri-ureteric fat preserved to ensure adequate ureteric blood supply. The location on the bladder to position an extra-vesical anastomosis was shown in one small RCT to be advantageous at the posterior bladder rather than anterior position to facilitate future endoscopic manipulation if needed, and reported less hydronephrosis post stent removal [142]. In cases where donor ureter has been damaged at retrieval then pyelo-native-ureterostomy or pyelo-neo-cystotomy can be performed. Mono-filament absorbable sutures should be used for the urinary anastomosis to prevent stone formation around the suture material [143].

Summary of evidence	**LE**
A meta-analysis of two RCTs and 24 observational studies favoured the extra-vesical Lich-Gregoir technique for reduced overall complications.	1a
A multi-centre prospective comparison study found the incidence of overall complications was similar for pyelo- and uretero-ureteral anastomosis and that for both procedures no graft was lost due to urological complications.	2b

Recommendations	**Strength rating**
Perform Lich-Gregoir-like extra-vesical ureteric anastomosis technique to minimise urinary tract complications in renal transplant recipients with normal urological anatomy.	Strong
Pyelo/uretero-ureteral anastomosis is an alternative especially for a very short or poorly vascularised transplant ureter.	Strong

Transplant ureteric anastomosis can be performed with or without a ureteric stent. If a stent is placed a second procedure is generally required for removal. A Cochrane review [144] concluded that stents are recommended to reduce major urological complications, especially urinary leak. The optimal timing for stent removal has yet to be defined [145]. A meta-analysis of five RCTS including 568 kidney transplantation patients showed a significant reduction in UTIs for early (≤ 7 days) vs. late removal (≥ 14 days) [146]. No significant differences where observed between the two groups in relation to post-operative complications such as ureteral stricture, ureteral obstruction, and ureteral leakage [146]. A second meta-analysis including 3,612 patients also reported a significant reduction in UTIs with early stent removal (< 3 weeks) vs. late removal (> 3 weeks) [147]. No significant differences where observed between the two groups regarding the incidents of ureteral stenosis and ureteral leakage [147].

Most commonly, stents are removed with local anaesthetic flexible cystoscopy unless there is a need to combine with another procedure warranting general anaesthetic. Various techniques to reduce the morbidity of a second procedure involve tying the stent to the catheter or use of percutaneous stents [148].

Recommendation	**Strength rating**
Use transplant ureteric stents prophylactically to prevent major urinary complications.	Strong

Duplex ureters are not infrequently identified at organ retrieval/kidney benching or during work-up for LDN [149, 150]. Duplex ureters can be anastomosed together and then joined to the bladder as one unit (double pant) or kept as two separate anastomoses. This also applies to the two single ureters in DKT in adults or with *en-bloc* transplantation from paediatric donors. The arguments for two separate ureteric anastomoses to the bladder are that an already tenuous blood supply may be further compromised with added suturing and handling, and if there is an issue with one ureter the other should remain unaffected. The advantages to forming one single (two ureter) anastomosis to the bladder are that only one cystotomy is needed; it may be faster and complications may be reduced. There is a lack of high-quality evidence relating to duplex ureters.

Recommendation	**Strength rating**
Use the same surgical principals for single ureters to manage duplex ureters and anastomose them either separately or combined.	Strong

3.1.5.5 *Transplantation/ureteric implantation in abnormal urogenital tract*

The following points should be considered when performing kidney transplantation in the abnormal urogenital tract:

- In patients with an ileal conduit, a kidney transplant may be placed upside down to align the ureter to the conduit and avoid a redundant ureter [151].
- The technique used to implant transplant ureter(s) into an ileal conduit is the same as the method used with native ureter(s) (Bricker; Wallace).
- In bladder augmentation or continent pouches, ureters should be implanted with a tunnel technique or extra-vesically (Lich-Gregoir). The latter is favoured in most patients.
- In patients with a Mitrofanoff catheterisable stoma or continent ileo-caecal pouch with catheterisable stoma, consideration should be given to the positioning of the catheterisable stoma (umbilical or iliac fossa - usually right-side) with clear communication with the transplant surgeons so that the position of any future transplant kidney is not compromised. If an intra-peritoneal placement of a future kidney transplant is likely, then placement of a Mitrofanoff exiting in the iliac fossa is preferable at the umbilicus. If a future kidney transplant is likely in the right iliac fossa then placement of a Mitrofanoff exiting at the umbilicus or left iliac fossa may be preferable.

3.1.6 ***Donor complications***

Living-donor nephrectomy, like any other intervention, is potentially associated with complications and mortality. However, the fact that the operation is performed on a healthy individual amplifies the relevance of any complications. Potential complications should be included in the process of informed consent.

Reported surgical mortality is 0.01% to 0.03% with no apparent alteration due to changes in surgical techniques or donor selection in recent years [152, 153]. According to a recent systematic review (190 studies) and meta-analysis (41 studies) on complications in minimally invasive LDN, reporting on a total of 32,308 LDNs, intra-operative complications occur in 2.2% (the most common being bleeding in 1.5% and injury to other organs in 0.8%) and post-operative complications occur in 7% (infectious complications in 2.6% and bleeding in 1%) [152]. Conversion to open surgery was reported in 1.1%, half due to bleeding and half due to injury to other organs. Surgical re-interventions occurred in 0.6%; the majority due to bleeding or to evacuate a haematoma [152]. A low trigger for conversion or re-operation should be observed in order to minimise the risk of serious complications.

A recent review looked for complications in 14,964 LDNs performed in the U.S. from 2008-2012 and found an overall peri-operative complication rate of 16.8%, gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%), surgical/anaesthesia-related injuries (2.4%), and “other” complications (6.6%). Among the sample, 2.4% required intensive care and in-hospital mortality was 0.007% [16].

Major Clavien Classification of Surgical Complications grade IV or higher affected 2.5% of donors. Risk factors for Clavien grade IV or higher events included obesity (adjusted odds ratio [aOR] 1.55, $p = 0.0005$), pre-donation haematologic (aOR 2.78, $p = 0.0002$), psychiatric conditions (aOR 1.45, $p = 0.04$) and robotic nephrectomy (aOR 2.07, $p = 0.002$). An annual centre volume > 50 (aOR 0.55, $p < 0.0001$) was associated with lower risk [16].

3.1.6.1 *Long-term complications*

Long-term complications are mostly related to the single-kidney condition. Renal function in living donors decreases after donation before improving for many years; however, in the long run it shows signs of slight deterioration [154-156]. There is a steady increase in the incidence of proteinuria; hypertension post-transplant having been shown as the main cause of increased albumin excretion [157].

The overall incidence of end-stage renal disease (ESRD) (0.4-1.1%) does not differ from the general population [154, 155, 158, 159]. According to a recent large retrospective study, the majority of ESRD developing after living kidney donation is due to new-onset disease that would have affected both kidneys [160]. However, there are some identified risk factors for deterioration of renal function after donation. According to a recent study that evaluated 119,769 live kidney donors in the United States, obese (BMI > 30) living kidney donors have a 1.9-fold higher risk for ESRD compared to their non-obese counterparts [161]. Long-term risk of death is no higher than for an age- and co-morbidity-matched population [153, 158].

Health related quality of life (HRQoL), including mental condition, remains on average better than the general population after donation [158, 159, 162]. However, some donors experience significant deterioration in their perceived QoL [162]. While global HRQoL is comparable or superior to population normative data, some factors identifiable around time of donation including longer recovery, financial stressors, younger age, higher BMI, lower education, smoking and higher expectations prior to donation, may identify donors more likely to develop poor HRQoL, providing an opportunity for intervention [158, 159, 162]. It is paramount that a careful

risk–benefit assessment is done and that proper information is given to the prospective donor, this should also include recommendations on health-promoting behaviour post-donation [163].

Summary of evidence	LE
A systematic review and meta-analysis on complications in minimally invasive LDN concluded that the techniques used for minimally invasive LDN are safe and associated with low complication rates.	1a
Survival rates and risk of end-stage renal disease are similar to those in the general population whilst donors HRQoL remains on average better than the general population.	2b

Recommendations	Strength rating
Restrict living donor nephrectomy to specialised centres.	Strong
Offer long-term follow-up to all living kidney donors.	Strong

*3.1.7 **Recipient complications***

3.1.7.1 General complications

Surgical complications during and after kidney transplantation may expose the recipient to an increased risk of morbidity and mortality. The incidence and management of such complications is therefore of primary importance [138, 145, 164-176]. We herein describe in detail the most common surgical complications in renal transplantation.

3.1.7.2 Haemorrhage

Haematomas are usually a minor complication in renal transplantation. Their incidence is reported to be between 0.2-25% [177, 178]. Small and asymptomatic haematomas do not usually require any intervention. In case of larger haematomas, clinical signs and symptoms due to external pressure with graft dysfunction and/or thrombotic graft vessel complications can be present. These cases may be treated by percutaneous drainage under computed tomography (CT) or ultrasound (US) guidance or may require surgical treatment [177].

3.1.7.3 Arterial thrombosis

Transplant renal artery thrombosis is a rare complication with a prevalence ranging from 0.5-3.5% [179]. Usually, it is a consequence of a technical error during the anastomosis although other causes may be related to both the donor and recipient's artery condition (i.e. atherosclerosis), intimal rupture during kidney harvesting, acute rejection episodes, external compression by haematoma or lymphocele, hypercoagulative state, severe hypotension, and toxicity of immunosuppressive agents (cyclosporine or sirolimus) [180]. The clinical manifestations are acute reduction of urine output and the elevation of renal function tests, often resulting in graft loss [177]. The diagnosis is obtained with eco-colour-Doppler [177]. Surgical exploration is usually recommended to evaluate the status of the graft. In the rare event the graft appears salvageable, a thrombectomy must be performed. In this situation, the iliac artery is clamped and an arteriotomy vs. a dissection of the vascular anastomosis must be performed in order to remove the clot. The graft can be flushed *in-situ* and re-vascularised [177]. Unfortunately, in the majority of the situations, the graft is not perfused and therefore an allograft nephrectomy must be performed [177, 181]. Alternatively, thrombolytic agent administration through a catheter directly into the transplant renal artery can be an efficient treatment, after the first ten to fourteen post-transplantation days [177].

Summary of evidence	LE
The diagnosis of renal artery thrombosis depends on eco-colour-Doppler followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal artery thrombosis.	2b

Recommendations	Strength rating
Perform ultrasound-colour-Doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Strong
Perform a surgical thrombectomy in case of a salvageable graft if arterial thrombosis is confirmed intra-operatively.	Weak
Perform an allograft nephrectomy in case of a non-viable graft.	Strong

3.1.7.4 Venous thrombosis

Transplant renal vein thrombosis is an early complication (prevalence 0.5-4%) and one of the most important causes of graft loss during the first post-operative month [182]. The aetiology includes technical errors and/or difficulties during surgery [177] and the hypercoagulative state of the recipient [183, 184]. Colour-Doppler-flow-ultrasonography shows absence of venous flow with an abnormal arterial signal (usually a plateau-like reversed diastolic flow). Furthermore, it is common to see an enlargement of the graft due to venous congestion [185]. Surgical exploration is usually recommended despite the fact that the majority of the cases will result in graft loss. In those cases where the venous thrombosis has not resulted in kidney loss at surgical exploration, a venotomy with surgical thrombectomy after clamping the iliac vein can be performed. Alternatively, an explantation and subsequent re-implantation can be considered [177]. Thrombolytic agents can also be used; however, their results have not been satisfactory [177, 186, 187].

Summary of evidence	**LE**
The diagnosis of renal vein thrombosis depends on colour-Doppler-flow-ultrasonography followed by surgical exploration to assess the status of the graft.	2b
Thrombectomy in the case of a viable graft and allograft nephrectomy in the case a non-viable graft are the treatment options for renal vein thrombosis.	2b

Recommendations	**Strength rating**
Perform ultrasound-colour-Doppler in case of suspected graft thrombosis.	Strong
Perform surgical exploration in case of ultrasound finding of poor graft perfusion.	Weak
If venous thrombosis is confirmed intra-operatively, perform a surgical thrombectomy in case of a salvageable graft or an allograft nephrectomy in case of a non-viable graft.	Weak
Do not routinely use pharmacologic prophylaxis to prevent transplant renal vein thrombosis.	Strong

3.1.7.5 Transplant renal artery stenosis.

The incidence of transplant renal artery stenosis is 1-25% [188, 189]. Risk factors include small calibre and atherosclerosis of the donor artery, trauma to donor artery at procurement, absence of arterial patch, suturing technique (interrupted vs. continuous), and damage to the iliac artery during transplantation [190, 191]. It is more common at the site of the anastomosis [190, 191]. It can be suspected in case of arterial hypertension refractory to medical treatment and/or an increase in serum creatinine without hydronephrosis or urinary infection. The diagnosis is performed by US-colour-Doppler, showing a peak systolic velocity (PSV) of > 200 cm/s in the graft renal artery [190]. In cases of doubt a magnetic resonance angiogram or a CT angiogram can be performed [192]. It is important to determine whether the stenosis is haemodynamically significant or not. Usually, a stenosis of over 50% is considered a risk for kidney impairment [193]. In case of mild stenosis (< 50%) and absence of symptoms with no deterioration of the allograft, management is normally conservative; although, a strict follow-up with US-colour-Doppler and clinical parameters has to be adopted due to the possible risk of graft failure [190]. In cases of clinically significant stenosis and/or > 50% on US-colour-Doppler, a confirmatory angiogram should be performed. If confirmed and a decision to treat is taken, treatments include percutaneous transluminal angioplasty/stent or surgical intervention. Interventional radiology is typically the first choice although patients considered unsuitable for radiological angioplasty due to recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty may benefit from surgical treatment [190, 191].

Summary of evidence	**LE**
Suspect transplant renal artery stenosis in case of refractory arterial hypertension and/or increasing serum creatinine without hydronephrosis/infection.	3
The diagnosis for transplant renal artery stenosis is by US-colour-Doppler, showing a peak systolic velocity of > 200 cm/s in the graft renal artery.	2a
Interventional radiology is the first-line treatment option for transplant renal artery stenosis; however, in patients considered unsuitable for radiological angioplasty surgical treatment may be considered.	3

Recommendations	**Strength rating**
Perform ultrasound-colour-Doppler to diagnose an arterial stenosis, in case of undetermined results on ultrasound consider a magnetic resonance or computed tomography angiogram.	Strong

Perform percutaneous transluminal angioplasty/stent, if feasible, as first-line treatment for an arterial stenosis.	Strong
Offer surgical treatment in case of recent transplant, multiple, long and narrow stenosis, or after failure of angioplasty.	Strong

3.1.7.6 Arteriovenous fistulae and pseudo-aneurysms after renal biopsy

Percutaneous biopsy may result in arteriovenous (AV) fistulae and/or intra-renal pseudo-aneurysms in 1-18% of cases [194]. The aetiology of the AV fistula is related to the simultaneous injury of adjacent arterial and venous branches. A pseudo-aneurysm occurs when only the arterial branch is damaged. Both conditions are diagnosed with US-colour-Doppler [177]. The majority of AV fistulae are asymptomatic, resolving in one to two years spontaneously, whilst approximately 30% of them persist and become symptomatic. Typically, the symptoms are hypertension, haematuria, and graft dysfunction due to shunting between arterial and venous vessels. There is an increased risk of spontaneous rupture in case of enlarging pseudo-aneurysms. For both AV fistulae and pseudo-aneurysm, angiographic selective or super selective embolisation represents the treatment of choice [195]. Partial or radical allograft nephrectomy is currently considered the last option [177].

Recommendations	**Strength rating**
Perform a ultrasound-colour-Doppler if a arteriovenous fistulae or pseudo-aneurysm is suspected.	Strong
Perform angiographic embolisation as first-line treatment in symptomatic cases of arteriovenous fistulae or pseudo-aneurysm.	Strong

3.1.7.7 Lymphocele

Lymphocele is a relatively common (1-26%) complication [196]. There is a significant aetiological association with diabetes, mammalian target of rapamycin (mTOR) inhibitors (i.e. sirolimus) therapy, and acute rejection [197]. For large and symptomatic lymphocele, laparoscopic fenestration is associated with the lowest overall recurrence (8%) and complication (14%) rate compared to open surgery and aspiration therapy [198]. Placement of a percutaneous drain (i.e. Pig-Tail) is an option with a success rate as high as 50% [163]. Percutaneous aspiration can be performed although the recurrence rate can be as high as 95% [198], with an increased risk of local infection (6-17%) [198]. Furthermore, sclerosant agents such as ethanol, fibrin sealant, gentamicin, or octreotide reduce the recurrence rate compared to simple aspiration [198, 199].

Recommendations	**Strength rating**
Perform percutaneous drainage placement as first-line treatment for large and symptomatic lymphocele.	Strong
Perform fenestration when percutaneous treatments fail.	Strong

3.1.7.8 Urinary leak

Urinary leakage occurs in 0-9.3% of cases [200]. Anastomotic urine leaks can be ureteral or vesical [201]. Ureteral necrosis and/or suture failure are the most important causes [202, 203]. Non-technical risk factors include recipient age, number of renal arteries, site of arterial anastomosis, occurrence of acute rejection episodes, bladder problems, and immunosuppressive regimen [204]. Urinary leak can be suspected by the urine output and the creatinine level in the drain fluid [202]. In order to decrease the risk of ureteral necrosis, it is important to preserve vascularisation of the distal ureter [202]. Furthermore, the routine use of a JJ-stent is recommended [203, 205]. The management of urinary leak depends on the location (renal pelvis, proximal or distal ureter, and bladder), the time of appearance and the volume of the leak. For early and low volume urine leaks the treatment may be conservative (i.e. urethral catheter, percutaneous nephrostomy and JJ-stent) [206]. In case of failure of the conservative management, or massive leak, surgical repair must be undertaken. Ureteral re-implantation directly to the bladder or to the native ureter provide similar results [141, 206].

Summary of evidence	**LE**
Suspect urinary leakage based on the urine output and the creatinine level in the drain fluid.	3
For early and low volume urine leaks conservative management may be considered.	3
Surgical repair should be undertaken when conservative management fails or massive urine leak occurs.	2b

Recommendations	Strength rating
Manage urine leak by JJ-stent and bladder catheter and/or percutaneous nephrostomy tube.	Strong
Perform surgical repair in cases of failure of conservative management.	Strong

3.1.7.9 Ureteral stenosis

Ureteral stenosis is a common complication in recipients, with an incidence of 0.6-10.5% [207]. Early stenosis (within three months of surgery) is usually caused by surgical technique or compromised ureteral blood supply during surgery. Late stenosis (after > six months) is provoked by infection, fibrosis, progressive vascular disease and/or rejection [202, 208]. Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function. The first approach in the management of stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram [207]. The following treatment options depend mainly on the timing, recoverable kidney function, anatomy of the stricture, patient body habitus/comorbidities, and surgeon preference. Strictures < 3 cm in length may be treated endoscopically either with percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision. In this scenario the success rate approaches 50%; although, maximum success is obtained for strictures < 1 cm [209-211]. In case of a recurrence after a primary endourological approach and/or stricture > 3 cm in length, surgical reconstruction should be performed [208] including direct ureteral re-implantation, pyelo-vesical re-implantation (with or without psoas hitch and/or Boari Flap) or in cases with a normal native ureter, uretero-ureterostomy [212, 213]. Long-term graft and patient survival are not significantly affected [214].

Summary of evidence	LE
Clinically significant ureteral stricture should be considered when persistent hydronephrosis on US occurs in association with impaired renal function.	3
The first approach in the management of a stricture is the placement of a percutaneous nephrostomy tube with an antegrade pyelogram.	2b
Strictures < 3 cm in length may be treated endoscopically.	3
For strictures > 3 cm in length or those which have reoccurred following a primary endourological approach surgical reconstruction should be performed.	2b

Recommendations	Strength rating
In case of ureteral stricture, place a nephrostomy tube for both kidney decompression and stricture diagnosis via an antegrade pyelogram.	Strong
Manage strictures < 3 cm in length either with surgical reconstruction or endoscopically (percutaneous balloon dilation or antegrade flexible ureteroscopy and holmium laser incision).	Strong
Treat late stricture recurrence and/or stricture > 3 cm in length with surgical reconstruction in appropriate recipients.	Strong

3.1.7.10 Haematuria

The incidence of haematuria ranges from 1-34% [200]. According to the literature, the Lich-Gregoire technique provides the lowest incidence of haematuria. Furthermore, meticulous haemostasis during re-implantation results in minimal bleeding [138, 200, 201]. Bladder irrigation is the first-line treatment. Some cases require cystoscopy with evacuation of clots and/or fulguration of bleeding sites [200].

3.1.7.11 Reflux and acute pyelonephritis

The frequency of vesicoureteral reflux is between 1-86% [200, 215]. Acute graft pyelonephritis occurs in 13% of graft recipients. Patients with lower tract urinary infections and cytomegalovirus (CMV) infection present a higher risk of acute graft pyelonephritis [216]. Endoscopic injection of dextranomer/hyaluronic acid copolymer may be the first approach for treatment of vesicoureteral reflux associated with acute pyelonephritis, with a success rate ranging from 57.9% after the first injection to 78.9% after the second injection [217]. Ureteral re-implantation or pyelo-ureterostomy with the native ureter is a viable second treatment option [212].

Recommendation	Strength rating
Use an endoscopic approach as first-line treatment for symptomatic reflux.	Weak

3.1.7.12 Kidney stones

Urolithiasis occurs in 0.2-1.7% of recipients [218, 219]. The most frequent causes are hyper filtration, renal tubular acidosis, recurrent UTIs, hypocitraturia, hyperuricaemia, hyperuricemia, excessive alkaline urine, persistent tertiary hyperparathyroidism and ureteral strictures [220, 221]. Another risk factor can be urinary anastomosis, with the lowest stone rate using Lich-Gregoir technique [219]. The most frequent clinical signs are fever, increased serum creatinine level, decreased urine output, and haematuria. Pain is usually not referred to due to impaired innervation. A US examination usually provides the diagnosis although a CT of the kidneys, ureters and bladder may be needed to confirm the location and size of the stone [220]. The management depends on the location and size of the stone, and the presence of obstruction. In case of obstructive stones first-line treatment includes placement of a nephrostomy tube, or in some occasions a JJ-stent [222]. Extracorporeal shock wave lithotripsy (ESWL) is usually considered the first approach for stones < 15 mm with stone-free rates varying between 40 and 80% depending on the location of the stone [222]. Ureteroscopy, including antegrade and retrograde approaches, can be considered for stones < 20 mm, with a success rate of up to 67% [140, 219, 223]. For larger stones (> 20 mm), percutaneous nephrolithotomy (PNL) can be offered with high overall effective stone-free rates. In cases of large impacted stones, uretero-ureteral anastomosis, pyelo-ureteral anastomosis, or uretero-vesical re-implantation may provide excellent results for both stone and ureteral obstruction [219].

Summary of evidence	**LE**
Extracorporeal shockwave lithotripsy should be considered as the first-line treatment option for stones < 15 mm.	2b
Antegrade/retrograde ureteroscopy and PNL may be considered as treatment options as they provide high stone-free rates.	2b
For larger stones (> 20 mm), PNL can be offered with a high overall effective stone-free rate.	2b

Recommendations	**Strength rating**
Evaluate the causes of urolithiasis in the recipient.	Strong
Treat ureteral obstruction due to a stone with a percutaneous nephrostomy tube or JJ-stent placement.	Strong
Perform shockwave lithotripsy or antegrade/retrograde ureteroscopy for stones < 15 mm.	Strong
Perform percutaneous nephrolithotomy for stones > 20 mm.	Weak

3.1.7.13 Wound infection

Wound infections occur in about 4% of cases. Risk factors include recipients > 60 years, high BMI, anaemia, hypo-albuminemia, long surgical times (> 200 min) [224]. Bacteria commonly involved are *Enterobacteriaceae, Staphylococcus aureus* and *Pseudomonas* [212]. Subcutaneous sutures, pre-dialysis transplantation, sealing or ligation of lymphatic trunks, prophylactic fenestration, reducing corticosteroid load, and avoiding sirolimus/everolimus therapy can decrease wound complication rates [224].

3.1.7.14 Incisional hernia

Incisional hernia occurs in approximately 4% of open kidney transplantations. Risk factors include age, obesity, diabetes, haematoma, rejection, re-operation through the same transplant incision and use of m-TOR inhibitors. Mesh infection is a risk factor for incisional hernia recurrence [225]. Open and laparoscopic repair approaches are safe and effective [225].

3.1.8 ***Urological malignancy and renal transplantation***

The following section is limited to a synopsis of three systematic reviews conducted by the EAU Renal Transplantation Panel.

3.1.8.1 Malignancy prior to renal transplantation

3.1.8.1.1 In the recipient

Standard procedure for transplant candidates includes systematic screening for the presence of any active/latent cancer or a past history of cancer. In candidates with a previous history of urological cancer, it can be challenging to decide if patients are suitable for transplantation and, if so, how long the waiting period prior to transplantation should be. To date, the waiting period has been primarily based on the Cincinnati Registry, which takes into account the type of tumour and the time between its treatment and kidney transplantation. However, the Cincinnati Registry has potential drawbacks as it does not consider the epidemiology of tumours

or that diagnostic and therapeutic procedures/tests have changed over time and that prognostic tools have improved. Additionally, treatment and the staging of the disease are not defined.

According to a recent systematic review the risk of tumour recurrence was similar between transplantation (n=786) and dialysis (n=1,733) populations for renal cell carcinoma (RCC) and prostate cancer (PCa). This was especially true for low grade/stage PCa, for which the risk of recurrence was low and consistent with nomograms [226]. For low stage/grade RCC the recurrence rate was significant for both dialysis and renal transplantation; however, recurrences were actually contralateral RCC with no impact on patient or graft survival [226].

Testicular cancer had a low risk of recurrence but case reports highlighted the possibility of late recurrence even for stage I tumours [226].

For urothelial carcinoma, studies were mainly related to upper urinary tract carcinomas in the context of aristolochic acid nephropathy for which the rate of synchronous bilateral tumour was 10-16% and the rate of contralateral recurrence was 31-39% [226].

These findings imply that a kidney transplant candidate with a history of appropriately treated low stage/grade PCa (PSA ≤ 10, Gleason score ≤ 6 and T1/T2a) or low grade T1 RCC could be listed for renal transplantation without any additional delay compared to a cancer-free patient. However, as the level of evidence was low, more studies are needed to standardise waiting periods before renal transplantation.

Summary of evidence	**LE**
Renal Cell Carcinoma	
The recurrence rates for transplanted vs. dialysed patients at <1, 1–5, and > 5 years were 0–8% vs. 0%, 0–27% vs. 0–9% and 0–41% vs. 0–48%, respectively.	2b
Overall five year survival rates for transplantation vs. dialysed patients were 80–100% vs. 76–100%, respectively.	
Prostate Cancer	
The recurrence rates for transplantation patients at <1 and > 5 years were 0–9% and 4–20%, respectively.	2b
Overall, 1–5 year survival rates for transplantation patients ranged from 62% to 100%.	

Recommendation	**Strength rating**
List for renal transplantation patients with a history of appropriately treated low stage/grade renal cell carcinoma or prostate cancer without additional delay.	Weak

3.1.8.1.2 In the potential donor kidney

In the general population, RCC constitutes 3% of all malignancies, with the incidence being highest in patients aged > 60 years. The current increasing age of donors may lead to a higher number of incidental RCCs found in donor kidneys and could theoretically decrease the number of kidneys suitable for transplantation. The main surgical approach to these kidneys is *ex vivo* tumour excision on the back-table with an oncological margin, frozen section biopsy, bench surgery renorraphy, and finally transplantation in the conventional fashion [227].

A recent systematic review assessed the effectiveness and harms of using kidneys with small renal tumours, from deceased or living donors, as a source for renal transplantation and it reported that five year overall and graft survival rates were 92% and 95.6%, respectively [227]. Tumour excision was performed *ex vivo* in all cases except for two (107/109 patients), and the vast majority of excised tumours were RCCs (88/109 patients), with clear-cell subtype the most common [227]. This systematic review, although with low-level evidence, suggested that kidneys with small renal masses are an acceptable source for renal transplantation and do not compromise oncological outcomes with similar functional outcomes to other donor kidneys.

Summary of evidence	**LE**
Tumour excision was performed *ex-vivo* in all cases except for two (107/109 patients).	2b
Overall survival rates at one, three and five years were 97.7%, 95.4%, and 92%, respectively.	
Mean graft survival rates at one, three and five years were 99.2%, 95%, and 95.6%, respectively.	

Recommendation	**Strength rating**
Do not discard a kidney for potential transplantation on the basis of a small renal mass alone.	Weak

3.1.8.2 Malignancy after renal transplantation

Cancer development after kidney transplant has become a major problem as it is one of the main causes of death in this population. Urological cancers, have an increased incidence after kidney transplantation partly due to the increasing age of recipients and their prolonged survival after transplantation.

Treatment of localised PCa following kidney transplantation is challenging due the presence of the kidney graft in the pelvic cavity close to the prostate. Two systematic reviews reported that oncological outcomes following PCa treatment in kidney transplant recipients are comparable to the non-transplanted population [228, 229] and surgery (radical prostatectomy), carried out in tertiary high-volume referral centres was the treatment choice in 75 to 85% of patients [228, 229]. Marra *et al*. reported cancer-specific survival rates of 96.8% for surgery, 88.2% for radiotherapy with androgen deprivation therapy and 100% for brachytherapy at mean follow-up of 24 months [229]. Hevia *et al*. reported five year cancer-specific survival of 97.5% for surgery, 87.5% for external beam radiation and 94.4% for brachytherapy [228].

Summary of evidence	**LE**
Surgery (radical prostatectomy) was the most frequently performed treatment for localised PCa after kidney transplant.	2b
Overall oncological outcomes following PCa treatment in kidney transplant recipients were comparable to the non-transplanted population.	2b

Recommendations	**Strength rating**
Be aware of the presence of a kidney transplant in the pelvis and the possibility of subsequent transplants when planning treatment for prostate cancer.	Strong
Refer kidney transplant patients with prostate cancer to an integrated transplant urology centre.	Strong

*3.1.9 **Matching of donors and recipients***

Histocompatibility antigens show remarkable polymorphism and human leukocyte antigen (HLA) matching is still very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches [230-233]. Human leukocyte antigen incompatibility can result in proliferation and activation of the recipient's CD4+ and CD8+ T-cells with concomitant activation of B-cell allo-antibody production. This may lead to cellular and humoral graft rejection. Matching should concentrate on HLA antigens, which impact outcome. Human leukocyte antigens A, B, C as well as DR must be determined in all potential recipients and donors according to current guidelines and national allocation rules [230-235]. Additionally, it is recommended to determine HLA-DQ antigens of donor and recipient. Furthermore, HLA-DP antigen characterisation may be performed, especially for sensitised recipients [230-235].

All patients registered for renal transplantation must have their serum screened for anti-HLA antibodies, which are particularly common after pregnancy, previous transplant, transplant rejection, and blood transfusions [230-235]. Thorough pre-transplant testing for HLA antibodies must be performed according to current recommendations [230-235]. Sera from potential organ recipients should be screened for HLA-specific antibodies every three months or as stipulated by the national and/or international organ exchange organisations [230-235]. In addition, screening for HLA-specific antibodies should be carried out at two and four weeks after every immunising event, e.g. blood transfusion, transplantation, pregnancy, and graft explantation [230-235]. Highly sensitised patients should have prioritised access to special allocation programmes [232, 233, 235], such as the acceptable mismatch (AM) programme of Eurotransplant [236]. A careful analysis of HLA antibody specificities must be carried out to avoid unacceptable HLA antigens and to determine acceptable HLA antigens in potential donors, who are expected to give a negative cross-match result. The definition of unacceptable HLA antigens should be implemented according to local allocation rules and international recommendations [230-234, 237]. The information on unacceptable HLA antigens should be highlighted with the patient's details in the database of the national kidney-sharing programme, preventing the unnecessary transport of kidneys to recipients with high antibody sensitivity.

To avoid hyper-acute rejection (HAR), adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation in accordance with national and international recommendations [230-233, 235].

Laboratories which provide HLA-testing, HLA antibody testing and cross-matching for transplant centres must have valid accreditation to ensure accuracy and reliability [224, 225, 230-232]. They must follow the standards of national and international organisations, such as the European Federation for Immunogenetics [235].

Previously, compatibility for ABO blood group antigens and HLA antigens was of critical importance in kidney transplantation. This may change in the future, e.g. in the new U.S. allocation system A2 and A2B donors are transplanted into B recipients [233]. To avoid an increasing imbalance between demand and supply in deceased donor kidney transplantation in O recipients, ABO identity is demanded by several organ allocation organisations with a few exceptions, e.g. as in zero HLA-A+B+DR-mismatch kidneys [233, 234]. With the introduction of antibody elimination methods, potent immunosuppression and novel agents (e.g. anti B-cell drugs), successful ABO-incompatible living donor transplantations, with good long-term outcomes are possible [238, 239]. However, higher costs and infection rates have been described.

Even the barrier of a positive cross-match due to preformed HLA antibodies is under discussion with newer "desensitisation" techniques available in cases with available living donors [240, 241]. Success rates are lower, antibody-mediated rejections are frequent, but survival may be better compared to waiting list survival on dialysis. While this is a rapidly evolving field, further research is needed to define standard protocols. Until then such "desensitisation" protocols are experimental and patients undergoing "desensitisation" should be treated in specialised centres, where outcomes are documented. Patients should be informed adequately of the risks and limitations and alternative strategies (e.g. acceptable mismatch programmes, cross-over transplantation and donor chains) should be discussed.

Summary of evidence	**LE**
Human leukocyte antigen matching is very important in kidney transplantation as transplant outcome correlates with the number of HLA mismatches. Matching should concentrate on HLA antigens, which impact outcome.	3
In accordance with national and international recommendations adequate (e.g. CDC, virtual) cross-match tests must be performed before each kidney and combined kidney/pancreas transplantation to avoid hyper-acute rejection.	3

Recommendations	**Strength rating**
Determine the ABO blood group and the human leukocyte antigen A, B, C and DR phenotypes for all candidates awaiting kidney transplantation.	Strong
Test both the donor and recipient for human leukocyte antigen DQ. Human leukocyte antigen DP testing may be performed for sensitised patients.	Strong
Perform thorough testing for HLA antibodies before transplantation.	Strong
Perform adequate cross-match tests to avoid hyper-acute rejection, before each kidney and combined kidney/pancreas transplantation.	Strong

*3.1.10 **Immunosuppression after kidney transplantation***

The principle underlying successful immunosuppression is 'the balance of survival'. Practitioners must prescribe a dosage of drug high enough to suppress rejection without endangering the recipient's health. Increased understanding of immune rejection has led to the development of safe modern immune suppression agents [242, 243], which suppress sensitised lymphocyte activity against a transplant. Immunosuppression is particularly important during the initial post-transplant period when there is a high incidence of early post-transplant rejection.

In later post-operative stages, 'graft adaptation' occurs, resulting in the very low rejection rates seen in maintenance patients. Rejection prophylaxis should therefore be reduced over time by steroid tapering and gradual lowering of calcineurin inhibitor (CNI) [242-244].

Non-specific side effects of immunosuppression include a higher risk of malignancy and infection, particularly opportunistic infections [242-244]. All immunosuppressants also have dose-dependent specific side effects. Current immunosuppressive protocols aim to reduce drug-specific side effects using a synergistic regimen. A truly synergistic regimen allows profound dose reductions of immunosuppressive drugs; therefore, reducing side effects whilst still maintaining efficacy due to the synergistic effects of the immunosuppressants.

The currently recommended standard initial immunosuppression regime provides excellent efficacy with good tolerability [242-245]. It is given to most patients and consists of:

- calcineurin inhibitors (preferably tacrolimus, alternatively cyclosporine);
- mycophenolate (MMF or enteric-coated mycophenolate sodium [EC-MPS]);
- steroids (prednisolone or methylprednisolone);
- induction therapy (preferably basiliximab in low and standard risk patients and anti-thymocyte globulin [ATG] in high-risk patients).

This multidrug regimen reflects the current standard of care for the majority of transplant recipients worldwide [242-244] and may be modified according to local needs and immunological risk. This standard regimen is likely to change as new immunosuppressive drugs and new treatment regimens are developed [242-244]. In addition, any initial drug regimen will need to be tailored to the individual needs of a patient as suggested by the appearance of side effects, lack of efficacy or protocol-driven requirements.

Recommendation	Strength rating
Perform initial rejection prophylaxis with a combination therapy of a calcineurin inhibitor (preferably tacrolimus), mycophenolate, steroids and an induction agent (either basiliximab or anti-thymocyte globulin).	Strong

3.1.10.1 Calcineurin inhibitors

Both cyclosporine and tacrolimus have significant side effects that are hazardous to the graft and patient [242-249]. Most importantly, both are nephrotoxic [250, 251], and long-term use is an important cause of chronic allograft dysfunction [252], eventually leading to graft loss or severe chronic kidney disease in recipients of non-renal organs. Both CNIs are considered to be 'critical-dose' drugs, so that any deviations from exposure can lead to severe toxicity or failure of efficacy. Due to their narrow therapeutic window and the potential for drug-to-drug interaction, CNIs should be monitored using trough levels, which provide a reasonable estimate for exposure [249].

Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival [242-248, 253, 254]. Tacrolimus provided better rejection prophylaxis and was associated with better graft survival, when censored for death in some analyses. Renal function was favourable for tacrolimus treated patients, in a number of trials [254-259]. Therefore, both CNIs can be used for the effective prevention of acute rejection, but due to higher efficacy tacrolimus is recommended by current guidelines as first-line CNI [243].

For both CNIs several different formulations are available [249, 260-268]. Tacrolimus once-daily dosing seems to be preferred by patients and is associated with better adherence and lower pharmacokinetic variability [249, 269, 270]. Precautions (e.g. close surveillance and determination of drug levels) should be instituted after conversion from one formulation to another [268, 271-275]. In case of specific side effects of a CNI (e.g. hirsutism, alopecia, gingival hyperplasia, diabetes, polyoma nephropathy) conversion to another CNI can be a successful strategy to reduce side effects [242-244, 276]. Due to differences in the efficacy and safety profile, the choice of CNI should include the individual risks and benefits for each patient.

Despite their side effects, CNIs have been a cornerstone of modern immunosuppressive regimens for more than thirty years as they have resulted in an exemplary improvement in kidney graft survival [242, 243]. Future protocols aim to minimise or even eliminate CNIs [244, 247, 249, 277-280]. However, until such strategies provide superior outcomes, CNIs remain the standard of care [242, 243, 281]. For severe CNI-related side effects, CNI withdrawal, replacement, or profound reduction may be needed [242, 244, 247, 277, 278]. Special attention should be paid to maintenance patients, who may need less CNIs than previously thought [242, 244, 249, 278, 279, 282].

Summary of evidence	LE
Meta-analysis of tacrolimus and cyclosporine has demonstrated similar outcomes with respect to overall patient and graft survival; however, tacrolimus provided better rejection prophylaxis.	1a
Due to differences in the efficacy and safety profile, the choice of CNI should take into account the immunological risk, characteristics, concomitant immunosuppression, and socio-economic factors of the recipient.	1

Recommendations	Strength rating
Use calcineurin inhibitors for rejection prophylaxis as they represent current best practice pending publication of long-term results using newer agents.	Strong
Use tacrolimus as first-line calcineurin inhibitor due to its higher efficacy.	Strong
Monitor blood-levels of both cyclosporine and tacrolimus to allow appropriate dose adjustment of calcineurin inhibitors.	Strong

3.1.10.2 Mycophenolates (MPA)

The mycophenolates, MMF and EC-MPS, are based on mycophenolic acid, which inhibits inosine monophosphate dehydrogenase (IMPDH) [283-287]. This is the rate-limiting step for the synthesis of guanosine monophosphate in the *de novo* purine pathway. As the function and proliferation of lymphocytes is more dependent on *de novo* purine nucleotide synthesis compared to other cell types, IMPDH inhibitors may provide more specific lymphocyte-targeted immunosuppression. The co-administration of MPA with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections [242, 245, 283-287]. Mycophenolic acid is not nephrotoxic; however, it inhibits bone marrow function and may cause CMV infections and gastrointestinal side effects, particularly diarrhoea [242, 245, 283-287]. There is also a higher incidence of polyoma nephropathy, especially when mycophenolate is combined with tacrolimus [288].

Both MPA formulations are equally effective with an almost identical safety profile [240, 278, 281, 283-286], though some prospective studies suggest a better gastrointestinal side-effect profile for EC-MPS in patients who have suffered from MMF-related gastrointestinal complaints, although firm evidence from prospective randomised studies is lacking [283-287, 289].

Mycophenolic acid is recommended by guidelines [243]. Standard doses in combination with cyclosporine are MMF 1 g or EC-MPS 720 mg twice daily, although higher initial doses have been suggested [242, 243, 283-287]. Despite its frequent use with tacrolimus, there is insufficient evidence to support the optimal dosage for this combination [242, 283, 285, 286, 290]. Tacrolimus has no influence on MPA exposure and leads to approximately 30% higher MPA exposure compared to cyclosporine. Most transplant centres use the same starting dose as in cyclosporine-treated patients, however dose reductions are frequent, especially because of gastrointestinal side effects. Weak evidence suggests that MPA dose reductions are associated with inferior outcomes, especially in cyclosporine treated patients [284-286, 291, 292]. Due to the high incidence of side effects, some centres perform a protocol-driven MPA dose reduction in tacrolimus treated patients [283, 285]. Regular monitoring for polyoma (BK virus) is recommended in patients given MPA combined with tacrolimus [242, 288].

Due to a higher incidence of CMV disease with MPA [287], either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted [242, 293]. Cytomegalovirus prophylaxis with antiviral medications (e.g. valganciclovir) should be used routinely in CMV positive recipients and in CMV negative recipients of CMV positive organ transplants, because prophylaxis has recently been shown to reduce CMV disease, CMV-associated mortality in solid organ transplant recipients, and leads to better long-term graft survival in kidney allograft recipients.

The benefit for MPA drug monitoring is uncertain and currently not recommended for the majority of patients [283, 285, 286, 294].

In maintenance patients, the potency of MPA can be used for successful steroid withdrawal in most patients [295] or for substantial dose reductions of nephrotoxic CNIs, which may lead to better renal function [242-245, 247, 278, 296]. Although there have been several studies of the potential for CNI-free protocols with MPA and steroids, complete CNI avoidance or withdrawal over the first three years has been associated with a substantially increased rejection risk and even worse outcomes in prospective randomised studies [242, 244, 278]. In contrast, CNI withdrawal under MPA and steroids appeared to be safe in long-term maintenance patients beyond five years post-transplant and resulted in improved renal function [242, 244, 247, 278, 296, 297].

Summary of evidence	LE
The co-administration of MPA with prednisolone and CNI has resulted in a profound reduction of biopsy-proven rejections.	1
Both MPA formulations, MMF and EC-MPS, are equally effective with an almost identical safety profile.	1
Due to a higher incidence of CMV disease with MPA either CMV prophylaxis or a pre-emptive strategy with regular screening for CMV viraemia should be instituted.	1

Recommendation	Strength rating
Administer mycophenolate as part of the initial immunosuppressive regimen.	Strong

3.1.10.3 Azathioprine

Mycophenolate is now routinely used as a primary therapy in place of azathioprine in most units worldwide. In comparison to azathioprine, MPA reduced rejection rates significantly in prospective randomised trials [242, 243, 245, 283-287]. Although a large, prospective study found that azathioprine may give acceptable results in a low-risk population [298], azathioprine is usually reserved for patients who cannot tolerate MPA [242, 243, 283, 284, 286]. When added to dual therapy with cyclosporine and steroids, a meta-analysis found no significant benefit for azathioprine with respect to major outcome parameters [299].

Recommendation	Strength rating
Azathioprine may be used in a low-risk population as an immunosuppressive drug, especially for those intolerant to mycophenolate formulations.	Weak

3.1.10.4 Steroids

Steroids have a large number of side effects [242-244, 295], especially with long-term use. Most practitioners still consider steroids (either prednisolone or methylprednisolone) to be a fundamental adjunct to primary immunosuppression, even though successful steroid withdrawal has been achieved in the vast majority of patients in many prospective, randomised trials [242, 244, 245, 295, 300, 301]. The risk of steroid withdrawal depends on the use of concomitant immunosuppressive medication, immunological risk, ethnicity, and time after transplantation. Although the risk of rejection diminishes over time, potential benefits may be less prominent after a prolonged steroid treatment period [242-245, 295]. Recent studies suggest similar efficacy but less diabetes after early steroid withdrawal or steroid minimisation in low-risk patients treated with tacrolimus, MPA and induction (either basiliximab or ATG) [302, 303].

Recommendations	Strength rating
Initial steroid therapy should be part of immunosuppression in the peri-operative and early post-transplant period.	Strong
Consider steroid withdrawal in standard immunological risk patients on combination therapy with calcineurin inhibitors and mycophenolic acid after the early post-transplant period.	Weak

3.1.10.5 Inhibitors of the mammalian target of rapamycin (m-TOR)

The immunosuppressants, sirolimus and everolimus, inhibit the mammalian target of rapamycin and suppress lymphocyte proliferation and differentiation [242, 277, 304-306]. They inhibit multiple intracellular pathways and block cytokine signals for T-cell proliferation. Similar effects are seen on B-cells, endothelial cells, fibroblasts, and tumour cells. Inhibitors of m-TOR are as effective as MPA when combined with CNIs in preventing rejection [242, 245, 277, 304-307]. However, m-TOR inhibitors exhibit dose-dependent bone marrow toxicity [242, 277, 304-306]. Other potential side effects include hyperlipidaemia, oedema, development of lymphoceles, wound healing problems, pneumonitis, proteinuria, and impaired fertility. The extensive side effect profile is responsible for inferior tolerability compared to MPA and potential differences in outcome in early years, when higher doses were used [308-313].

To date, no prospective comparative studies have been carried out on the m-TOR inhibitors sirolimus and everolimus [314]. Both m-TOR inhibitors have an almost identical side effect profile and mainly differ in their pharmacokinetic properties [242, 277, 304-306, 315]. Sirolimus has a half-life of about 60 hours, is given once a day and is licensed for prophylaxis in kidney recipients only. Everolimus has a half-life of about 24 hours, is licensed for kidney, liver and heart recipients and is given twice a day. Everolimus is licenced for use with cyclosporine and can be given simultaneously with cyclosporine, while sirolimus should be given four hours after cyclosporine. The pharmacological drug-drug interaction with cyclosporine is far less relevant for tacrolimus, resulting in the need for a higher starting dose of m-TOR inhibitors in combination with tacrolimus [258, 316, 317]. Sirolimus is also licensed in combination therapy with steroids for cyclosporine withdrawal from combination therapy with cyclosporine.

Therapeutic monitoring of trough levels is recommended because of the narrow therapeutic window and the risk of drug-to-drug interactions [242, 277, 304-306, 315].

When combined with CNIs, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia should be administered for one year following transplantation, e.g. low-dose cotrimoxazole [242, 304-306]. Most importantly, combination therapy with CNIs aggravates CNI-induced nephrotoxicity, although m-TOR inhibitors themselves are non-nephrotoxic [242]. Several studies suggest less favourable outcomes and increased drug discontinuations due to adverse events for this combination, especially if CNIs are maintained at standard dosages [242, 245, 247, 258, 307, 309, 310, 318-323]. Calcineurin inhibitor dosage should therefore be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy [277, 304-306, 312, 315].

Several studies suggest m-TOR inhibitors cannot replace CNIs in the initial phase after transplantation due to lower efficacy and a less favourable side effect profile, particularly wound healing problems and lymphoceles [240, 242, 243, 274, 298, 299, 304, 306, 314]. Other trials suggest that m-TOR inhibitors may replace CNI at later stages, e.g. three months after transplantation, with improvements in renal function, predominately in cyclosporine treated patients [242, 244, 245, 247, 256, 277, 304-306, 309, 310, 312, 324-326]. It is unclear if there is a real benefit in comparison to patients on tacrolimus and MPA [256, 325]. However, there is an increased risk of rejection and development of HLA antibodies [242, 244, 256, 277, 327], which may be offset by the benefit of the non-nephrotoxic immunosuppression. Patients treated with m-TOR inhibitors develop less leucopenia and opportunistic viral infections, especially less CMV infections compared to MPA [258, 309, 312, 322-324, 328].

Proteinuria and poor renal function at conversion are associated with inferior outcomes [242, 244, 277, 304-306]. Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.

Due to an anti-proliferative effect and a lower incidence of malignancy in m-TOR inhibitor treated patients, conversion from CNIs to m-TOR inhibitors may be beneficial for patients, who develop malignancy after transplantation, or who are at a high risk for the development of post-transplant malignancy or skin cancer [242, 244, 277, 304-306, 311-313, 329-332]. Several studies and case reports have suggested that patients with Kaposi sarcoma under CNI therapy benefit from conversion to an m-TOR inhibitor [330].

In summary, m-TOR inhibitors are not recommended as initial immunosuppressive therapy due to their side effect profile and higher discontinuation rates [243]. However, m-TOR inhibitors are a well-studied alternative treatment option.

Summary of evidence	**LE**
Combination therapy with CNIs aggravates CNI-induced nephrotoxicity. Therefore, CNI dosage should be substantially reduced in combination therapy with m-TOR inhibitors, which seems to have no impact on efficacy, due to the highly synergistic potential of this combination therapy.	1
Take into consideration impaired wound healing and prophylactic surgical measures when m-TOR inhibitors are used as part of the initial immunosuppressive regimen or when patients treated with m-TOR inhibitors undergo major surgery.	1
When combined with CNIs, antimicrobial prophylaxis for *P. jirovecii* pneumonia should be administered for one year following transplantation.	1
Conversion from CNIs is not advisable in patients with proteinuria > 800 mg/day, and a cautious and individual approach should be followed in patients with GFR < 30 mL/min.	1

Recommendations	**Strength rating**
The m-TOR inhibitors may be used to prevent rejection in patients who are intolerant to standard therapy.	Weak
Significantly reduce calcineurin inhibitor dosage in a combination regimen with m-TOR inhibitors to prevent aggravated nephrotoxicity.	Strong
Do not convert patients with proteinuria and poor renal function to m-TOR inhibitors.	Strong
Monitor blood-levels of both sirolimus and everolimus to allow for appropriate dose adjustment.	Strong

3.1.10.6 Induction with Interleukin-2 receptor antibodies

Basiliximab, a high-affinity anti-interleukin-2 (IL-2) receptor monoclonal antibody is approved for rejection prophylaxis following organ transplantation [242, 243, 245, 333-337]. Basiliximab is given before

transplantation and on day four post-transplant. The drug is safe, and IL-2 receptor antibodies have been shown in RCTs to reduce the prevalence of acute cellular rejection by approximately 40% [242, 243, 245, 333-335]. Meta-analyses [245, 333-335] have confirmed the efficacy, although no positive effect on patient or graft survival could be demonstrated, large retrospective cohort studies and recent large prospective studies suggest such a benefit [242, 243, 338, 339]. Several large controlled trials support the efficacy and safety of quadruple therapy with tacrolimus, mycophenolate and steroids. Interleukin-2 receptor antibodies may allow early steroid withdrawal [295], although higher rejection rates were described in some studies. Most importantly, IL-2 receptor antibodies allow a substantial reduction in CNIs or steroids, while maintaining excellent efficacy and renal function [242-245, 302, 333-335]. Therefore, this regimen is proposed as first-line immunosuppression in patients with low to normal immunological risk [243, 339].

Recommendation	Strength rating
Use interleukin-2 receptor antibodies for induction in patients with normal immunological risk in order to reduce incidence of acute rejection.	Weak

3.1.10.7 T-cell depleting induction therapy

Prophylactic immunosuppression regimens in many countries, particularly the U.S., use potent T-cell depleting 'induction' treatments [242, 243, 245, 333, 338, 340-343]. Most frequently, ATG is used for prevention of rejection in immunological high-risk patients, as supported by meta-analysis [339], and recommended by guidelines [243, 344]. In addition, these potent biological agents are used for the treatment of severe, steroid resistant rejection episodes [340, 343].

Use of T-cell depleting antibodies in immunological low-risk patients has not been associated with improved long-term outcomes but with an increased risk of severe opportunistic infections and malignancy, particularly post-transplant lymphoproliferative disease [242, 243, 245, 333, 339-341]. Some centres use these agents to provide effective rejection prophylaxis in order to facilitate steroid withdrawal [302, 338, 342].

Recommendation	Strength rating
T-cell depleting antibodies may be used for induction therapy in immunologically high-risk patients.	Weak

3.1.10.8 Belatacept

Belatacept is a fusion protein, which effectively blocks the CD28 co-stimulatory pathway and thereby prevents T-cell activation [277, 345, 346]. Belatacept is intravenously administered and indicated for use as part of a CNI-free regimen together with basiliximab induction, MPA, and corticosteroids. Long-term data from three randomised studies of *de novo* kidney transplant recipients demonstrated better renal function vs. cyclosporine-based immunosuppression, although rates and grades of acute rejection were higher for belatacept in the first year post-transplant [242, 245, 257, 277, 345-351]. In patients receiving a standard deceased or living donor kidney, better graft survival was observed, while similar graft survival rates were found with ECDs. Interestingly, belatacept-treated patients had better preserved histology and developed less donor specific antibodies (DSA) compared to cyclosporine [352]. The long-term safety profile of belatacept treated patients was similar to cyclosporine controls, less belatacept treated patients developed metabolic complications or discontinued treatment due to adverse events [350, 351, 353, 354]. In addition, the option of converting patients (either stable patients or due to CNI or m-TOR associated toxicity) was explored with promising initial results [348, 355-357]. Specific safety signals include a higher rate of post-transplant lymphoproliferative disorder (especially in Epstein-Barr virus (EBV) negative patients), more herpes infections, and tuberculosis in patients from endemic areas [277, 345, 346]. Belatacept was approved in the U.S. and in Europe for EBV positive patients, but is not yet available in many countries. Additional studies are ongoing to fully explore the value of this compound.

Recommendation	Strength rating
Belatacept may be used for immunosuppressive therapy in immunologically low-risk patients, who have a positive Epstein-Barr virus serology.	Weak

*3.1.11 **Immunological complications***

Immunological rejection is a common cause of early and late transplant dysfunction [243, 358-362]. There is great variation in the timing and severity of rejection episodes and how they respond to treatment. Today two

main types of immunological reactions are distinguished, T-cell mediated rejections (TCMR) and antibody-mediated rejections (ABMR) [243, 358-360]. Antibody-mediated rejection and TCMR may be diagnosed together, called mixed acute rejection. Antibody-mediated rejection may occur as hyperacute rejection (HAR), active rejection or chronic rejection. Chronic ABMR is considered as one of the leading causes of late graft loss.

The ultimate standard for the diagnosis of rejection is transplant biopsy [243], because it is impossible to differentiate acute rejection solely on clinical indicators from other causes of renal dysfunction (e.g. acute tubular necrosis, infection, disease recurrence or CNI nephrotoxicity). Therefore, all rejections should be verified by renal biopsy and biopsies should be classified according to the most recent Banff criteria [363], which are the basis for prognosis and treatment [241, 358, 361]. Renal transplant biopsy should be conducted preferably under US control, using an automated needle biopsy system (e.g. Tru-Cut biopsy gun) [243, 358] with a 16 G needle to assure specimen adequacy. The biopsy procedure is considered safe but complications such as bleeding and AV fistulas may occur [243, 364, 365]. The reported risk of major complications (including substantial bleeding, macroscopic haematuria with ureteric obstruction, peritonitis or graft loss) is approximately 1%. Most important contraindications are anti-coagulant therapy including anti-platelet agents and uncontrolled hypertension.

Summary of evidence	LE
There must be routine access to US-guided biopsy of the transplant and sufficient expertise in the hospital pathology department to allow a rapid and clear-cut diagnosis of rejection or other type of allograft dysfunction.	2
Steroid treatment for rejection may start before the renal biopsy is performed.	2

Recommendations	Strength rating
Monitor transplant recipients for signs of acute rejection, particularly during the first six months post-transplant.	Strong
Take regular blood samples in addition to regular monitoring of urine output and ultrasound examinations in order to detect graft dysfunction during hospitalisation.	Strong
Immediately rule out other potential causes of graft dysfunction in cases of suspected acute rejection. An ultrasound of the kidney transplant should be performed.	Strong
Perform a renal biopsy, graded according to the most recent Banff criteria, in patients with suspected acute rejection episodes.	Strong
Only if contraindications to renal biopsy are present, can ‘blind’ steroid bolus therapy be given.	Strong
Test patients who suffer acute rejection as soon as possible for anti-HLA antibodies against the graft.	Strong
Reassess the immunosuppressive therapy of all patients with rejection, including patient adherence to the medication, which is of particular importance in late rejections.	Strong

3.1.11.1 Hyper-acute rejection

Hyper-acute rejection is the most dramatic and destructive immunological attack on the graft [230, 243, 358, 359]. It results from circulating, complement-fixing IgG antibodies, specifically reactive against incompatible donor antigen, which engages with and destroys the vascular endothelium within minutes or hours after vascularisation. It occurs in ABO-incompatible grafts due to the presence of high titres of pre-existing iso-antibodies against blood group antigens. In ABO-matched grafts, HAR is mediated by anti-donor HLA IgG antibodies. With the development of the cross-match test before transplantation, HAR has become an extremely uncommon complication [230]. Imaging and histology reveals generalised infarction of the graft, which has to be treated by graft nephrectomy. Therefore, prevention is crucial, either by avoidance of high iso-antibodies against incompatible blood group antigens in case of an ABO-incompatible renal transplant and/or by performing a regular cross-match before transplantation (see section 3.1.9).

Recommendation	Strength rating
Prevent hyper-acute rejection by adequate ABO blood group and HLA matching of donor and recipients.	Strong

3.1.11.2 Treatment of T-cell mediated acute rejection

As only a few randomised trials have investigated different treatment options for this clinical problem, therapy is mainly based on empirical experience rather than on clinical evidence [243, 343, 358, 366]. Parenteral methylprednisolone (500 mg to 1 g) should be given intravenously as one pulse per day for three days. Anuria or a steep rise in the serum creatinine may indicate steroid-refractory rejection and the need for another three day course of pulsed methylprednisolone therapy [243, 358]. In addition, baseline immunosuppression should be optimised to ensure adequate drug exposure [243, 358, 366]. In severe rejection, a conversion from cyclosporine to tacrolimus and/or from azathioprine to MPA is recommended [243, 358].

T-cell depleting biological agents, such as ATG may be given in severe steroid-refractory cases [243, 340, 343, 358, 366]. If biological agents are used, other immunological suppression should be adapted and daily T-cell monitoring should be considered to minimise the dose of the biological agent [340]. Before immunosuppression is intensified, especially before the use of T-cell depleting agents, the prognosis of the graft should be critically assessed against the risks of the aggravated immunosuppression. The patient should be counselled adequately.

Recommendations	**Strength rating**
Use steroid bolus therapy as first-line treatment for T-cell mediated rejection in addition to ensuring adequate baseline immunosuppression.	Strong
In severe or steroid-resistant rejection, use intensified immunosuppression, high-dose steroid treatment, and eventually T-cell depleting agents.	Strong

3.1.11.3 Treatment of antibody mediated rejection (ABMR)

Treatment of ABMR relies mainly on retrospective studies and empirical treatment guidelines [367]. Consensus is that it is important to classify the clinical and histological phenotype of the rejection in order to make adequate treatment decisions [367]. Important clinical factors are time of rejection (early acute < 30 days post-transplant vs. late), preformed vs. *de novo* donor-specific antibodies (DSA), and histology (active vs. chronic rejection).

For active ABMR due to pre-existing DSA treatment with a steroid bolus (at least three days of 500 mg/day) in combination with intravenous immunoglobulin (IVIG) and plasmapheresis or immune-adsorption is recommended. Intravenous immunoglobulin (IVIG) [243, 358, 368-373] may modulate and/or suppress antibody production. Intravenous immunoglobulin alone seems insufficient for effective treatment and IVIG is used today in a multimodal regimen. Dosages vary widely from 0.2-2.0 g/kg bodyweight, and no comparative studies (e.g. on the dose or optimal concomitant immunosuppression) have been published. Retrospective and prospective case series clearly suggest efficacy of antibody removal using plasmapheresis or immune-adsorption columns [243, 358, 368-373], although details of the procedures vary widely. Adjunctive therapies such as complement inhibitors, rituximab or splenectomy might be considered in severe early acute cases. Despite controversial data on the utility of anti-CD20 antibody [243, 343, 358, 368-373], rituximab may also be considered as adjunctive therapy in late active ABMR according to expert consensus. Although T-cell depleting agents such as ATG appear to have limited value they are frequently used during mixed acute rejection [241]. However, retrospective series suggests aggravated toxicity, when rituximab is combined with ATG [374], or steroids [343]. Furthermore, many centres will optimise maintenance therapy with MPA and steroids and sufficient tacrolimus trough levels should be achieved [243, 358, 368-370, 373].

Chronic acute mixed rejection due to pre-existent DSA has no specific treatment recommendations except for optimisation of maintenance therapy and eventually IVIG as an adjunctive treatment with a low level of evidence. In patients presenting with *de novo* DSA optimisation of maintenance, immunosuppression is recommended and non-adherence should be addressed and managed accordingly. If histology shows active ABMR plasmapheresis, rituximab and IVIG can be considered as potential adjunctive agents without good evidence from clinical trials. If biopsy demonstrates pure chronic ABMR no special treatment is recommended due to lack of convincing data, except for IVIG as potential treatment option without firm evidence. Treatment for chronic ABMR appears to be less successful [358, 368, 370].

In summary, several regimens have proven some efficacy in ABMR. However, except for a beneficial effect of early antibody removal, the lack of firm evidence does not permit evidence-based recommendations for treatment. As a consequence, prevention of ABMR by adequate pre-transplant screening, regular DSA monitoring, avoidance of suboptimal immunosuppression and reinforcement of adherence are crucial [230, 358, 372, 375].

Recommendation	Strength rating
Treatment of antibody mediated rejection should include antibody elimination.	Strong

*3.1.12 **Follow-up after transplantation***

Long-term graft function is of critical importance for the success of a transplant [243, 244]. Therefore, regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen. Complications of immunosuppression occur frequently including specific complications of the different drugs as well as over immunosuppression (namely opportunistic infections and malignancy) [243, 244]. The risk of cancer and cardiac disease is several-fold higher in transplanted patients than in the general population. Cancer is a cause of significant morbidity and mortality in the transplanted population [243, 376, 377]. Cardiovascular disease is the most frequent cause of death in renal allograft recipients [243, 378, 379]. Other important long-term problems are non-adherence, the development of anti-HLA antibodies, recurrence of the original disease and CNI associated nephrotoxicity [243, 244].

3.1.12.1 Chronic allograft dysfunction/interstitial fibrosis and tubular atrophy

Many patients lose their grafts due to chronic allograft dysfunction [243, 244, 380]. Histology will usually reveal a chronic process of interstitial fibrosis and tubular atrophy (IF/TA) [381]. Some patients will have immunological chronic ABMR [382], as discussed in section 3.1.11.3. Interstitial fibrosis and tubular atrophy takes months or years to develop and is heralded by proteinuria and hypertension, with a simultaneous or delayed rise in serum creatinine level over months [243, 380, 381]. It is likely that IF/TA is more common in patients who have had early attacks of acute rejection or infection. The main differential diagnosis is chronic nephrotoxicity [383], which is common in patients receiving CNIs, and pre-existing and/or aggravated chronic kidney damage from a marginal donor kidney [243, 380, 381].

Diagnosis is by renal biopsy [243, 380]. In patients diagnosed early, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen [201-203, 263, 264]. Conversion to m-TOR inhibitors is an option for patients without significant proteinuria (< 800 mg/day), but moderate renal function [242-244]. Alternatively, successful conversion to a mycophenolate based regimen has been described, especially in patients beyond the first three years post-transplant [242, 244, 278]. If there is intolerance to m-TOR inhibitors or MPA, conversion to belatacept or an azathioprine-based regimen may be successful, though the higher risk of rejection warrants close surveillance [357]. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA [244, 278].

In patients with proteinuria, intervention with an angiotensin converting enzyme inhibitor, or angiotensin II receptor blocker [243, 380] together with tight blood pressure control may slow down renal progression. Other supportive measures include the treatment of hypertension, hyperlipidaemia, diabetes, anaemia, acidosis, and bone disease [243]. However, ultimately, the patient will require another transplant (if fit enough to go on the transplant waiting list) or dialysis therapy.

Summary of evidence	LE
Regular long-term follow-up by experienced transplant physicians is essential in order to detect complications or graft dysfunction early and reassure adherence to the immunosuppressive regimen.	4
Annual screening should include a dermatological examination, cardiovascular history and exam, tumour screening (including a nodal examination, faecal occult screening, chest x-ray, gynaecological and urological examination), and an abdominal US, including US of the native and transplanted kidney. If appropriate, further diagnostic tests should be prompted to treat or slow down the progression of any identified complication.	4
In patients diagnosed early with IF/TA, particularly if there is evidence for CNI toxicity, disease progression may be slowed by conversion to a CNI-free regimen. If the risk of rejection seems too high, another option is substantial reduction of CNI under the protection of MPA.	1
Supportive measures should aim to adequately treat the consequences of chronic kidney disease (e.g. anaemia, acidosis, bone disease).	4

Recommendations	Strength rating
Provide lifelong regular post-transplant follow-up by an experienced and trained transplant specialist at least every six to twelve months.	Strong
Advise patients on appropriate lifestyle changes, potential complications, and the importance of adherence to their immunosuppressive regimen.	Strong

Regularly monitor (approximately every four to eight weeks) serum creatinine, estimated glomerular filtration rate, blood pressure, urinary protein excretion, immunosuppression and complications after renal transplantation. Changes in these parameters over time should trigger further diagnostic work-up including renal biopsy, a search for infectious causes and anti-HLA antibodies.	Strong
Perform an ultrasound of the graft, in case of graft dysfunction, to rule out obstruction and renal artery stenosis.	Strong
In patients with interstitial fibrosis and tubular atrophy undergoing calcineurin inhibitor (CNI) therapy and/or with histological signs suggestive for CNI toxicity (e.g. arteriolar hyalinosis, striped fibrosis) consider CNI reduction or withdrawal.	Strong
Initiate appropriate medical treatment, e.g. tight control of hypertension, diabetes, proteinuria, cardiac risk factors, infections, and other complications according to current guidelines.	Strong

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5. CONFLICT OF INTEREST

All members of the EAU Renal Transplantation Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

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1. INTRODUCTION

1.1 Aims and Objectives

The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines aim to provide a comprehensive overview of the medical aspects relating to sexual and reproductive health in adult men. These Guidelines cover the former EAU Guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

It must be emphasised that guidelines present the best evidence available to the experts. However following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - while taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Sexual and Reproductive Health Guidelines Panel consists of an international multi-disciplinary group of urologists, endocrinologists and a psychologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/sexualandreproductivehealth/.

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and android devices. These are abridged versions that may require consultation together with the full text version. All documents can be viewed through the EAU website:
http://www.uroweb.org/guideline/sexualandreproductivehealth/.

1.4 Publication History

This document is a further update of the 2021 Guidelines which already included a comprehensive update of the 2018 versions of Male Sexual Dysfunction, Male Infertility and Male Hypogonadism guidelines, along with several new topics. Additional sections will be added in the coming years to address male contraception, vasectomy, and penile cosmetic surgery, which have not previously been addressed.

1.5 Changes in the Guideline for 2022

The literature for the complete document has been assessed and updated, wherever relevant. Key changes in the 2022 publication:

- Section 3.4 - Classification and causes of male hypogonadism: update on effects of coronavirus 2 (SARS-CoV-2) infection (COVID-19);
- Section 5.6.2.8.1 – Treatment of Erectile Dysfunction - Platelet Rich Plasma: addition to the text and a new recommendation;
- Section 6.2.6.2.4 - Treatment of Premature Ejaculation – Tramadol: amendment to the text and amended recommendation;
- Section 8.2.3.1 - Conservative Treatment of Penile Curvature - Platelet Rich Plasma (PRP): addition to the text and new recommendation;
- Section 10.3 – Diagnostic Evaluation of Male Infertility: the text has been amended in light of the 6th edition of the WHO Manual for the Examination and Processing of Human Semen;
- Section 10.6.2 Male Infertility - Non-obstructive azoospermia: text and recommendation amended for indications and techniques of sperm retrieval relating to conventional and microdissection TESE.

2. METHODOLOGY

2.1 Methods

For the 2022 Sexual and Reproductive Health Guidelines, further new evidence has been identified, collated and appraised through a structured assessment of the literature.

For each recommendation within the Guidelines there is an accompanying online strength rating form; the basis of which is a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [1, 2]. Each strength rating form addresses several key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];

2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis that panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the term 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences. Additional information can be found in the general Methodology section of this print, and online at the European Association of Urology (EAU) website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at this address.

2.2 Review

The existing sections of the Sexual and Reproductive Health Guidelines were peer reviewed prior to publication in 2020. The new section for priapism was reviewed prior to publication in 2021.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2023 update of the Sexual and Reproductive Health Guidelines. Systematic reviews planned for 2022 are:

- Penile augmentation surgery;
- Vasectomy and male contraception;
- Penile prosthesis implantation peri-operative complications;
- Importance of psychology/psychosexology in the field of urology;
- Sexual function outcomes in men undergoing interventions for prostate cancer.

3. MALE HYPOGONADISM

3.1 Epidemiology and prevalence of male hypogonadism

Male hypogonadism is associated with decreased testicular function, with decreased production of androgens and/or impaired sperm production [5]. This is caused by poor testicular function or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis. Several congenital or acquired disorders causing impaired action of androgens are also described [5]. Hypogonadism may adversely affect multiple organ functions and quality of life (QoL) [6]. Late-onset hypogonadism (LOH) is a clinical condition in ageing men, which, by definition, must comprise both persistent specific symptoms and biochemical evidence of testosterone deficiency [5, 7]. Late-onset hypogonadism is frequently diagnosed in the absence of an identifiable classical cause of hypogonadism, which becomes more prevalent with age, usually occurring, but not exclusively, in men aged > 40 years.

Male hypogonadism has also been called *Testosterone Deficiency*. The Panel has agreed to use the term *Male Hypogonadism*, which may better reflect and explain the underlying pathophysiology. Likewise, the Panel has further agreed to continue with the term *testosterone therapy*. The present Guidelines specifically address the management of adult male hypogonadism also called LOH. Some insights related to congenital or pre-pubertal hypogonadism are also provided and summarised.

The prevalence of hypogonadism increases with age and the major causes are central obesity, other co-morbidities (e.g., diabetes) and overall poor health [8]. In healthy ageing men, there is only a small gradual decline in testosterone; up to the age of 80 years, aging accounts for a low percentage of hypogonadism [8]. In men aged 40-79 years, the incidence of symptomatic hypogonadism varies between 2.1-5.7% [9-11]. The incidence of hypogonadism has been reported to be 12.3 and 11.7 cases per 1,000 people per year [9, 12].

There is a high prevalence of hypogonadism within specific populations, including patients with type 2 diabetes (T2DM), metabolic syndrome (MetS), obesity, cardiovascular disease (CVD), chronic obstructive pulmonary disease, renal disease and cancer [11]. Low testosterone levels are common in men with T2DM [13] and a high prevalence of hypogonadism (42%) has been reported in T2DM patients [14].

Klinefelter syndrome, a trisomy associated with a 47,XXY karyotype, is the most prevalent genetic cause of primary hypogonadism (hypergonadotropic hypogonadism), with a global prevalence of 1/500-1,000 live male births [15-17]. However, < 50% of individuals with Klinefelter syndrome are diagnosed in their lifetime [18].

3.1.1 Body Composition and Metabolic Profile

Low testosterone levels are common in men with obesity. Male hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to men with adequate testosterone levels [19]. There is much evidence that a low testosterone level is strongly associated with increased visceral adiposity, but it also leads to lipid deposition in the liver and muscle and is associated with atherosclerosis [19]. *In vitro* studies have suggested that hypogonadism impairs glucose and triglyceride uptake into subcutaneous fat depots [19]. This enhances the uptake of glucose and triglycerides into ectopic fat depots.

Testosterone therapy has been associated with a reduced percentage of body fat and increase of lean body mass [20]. Data from a registry study have suggested that over a period of 11 years, testosterone therapy with long-acting intramuscular testosterone undecanoate was associated with a substantial but gradual loss of weight, along with a reduction in waist circumference [21]. Testosterone also reduces liver fat content and muscle fat storage [19].

3.1.2 Metabolic Syndrome/Type 2 Diabetes

Metabolic Syndrome (MetS) is characterised by several specific components, including increased waist circumference, dyslipidaemia, hypertension, and impaired glucose tolerance. Hypogonadism is associated with central obesity, hyperglycaemia, insulin resistance and dyslipidaemia [low high-density lipoprotein (HDL)] cholesterol, raised total and low-density lipoprotein (LDL) cholesterol and triglycerides], hypertension and predisposition to T2DM, which are all components of MetS [22].

Several randomised controlled trials (RCTs) have shown that testosterone therapy might improve insulin resistance and hyperglycaemia and lower cholesterol and LDL-cholesterol [23-27]. Testosterone therapy in hypogonadal T2DM improved glycaemic control in some RCTs and registry trials; however, there is no conclusive evidence from RCTs and meta-analyses [24, 28, 29]. A recent large placebo-controlled RCT, including 1,007 patients with impaired glucose tolerance or newly-diagnosed T2DM and total testosterone < 14 nmol/L, showed that testosterone therapy for 2 years reduced the proportion of patients with T2DM regardless of a lifestyle programme [30]. Similarly, a previously published registry study reported that testosterone therapy was associated in time with remission of T2DM [28]. HDL-cholesterol may decrease, remain unchanged or increase with testosterone therapy. Testosterone therapy in men with MetS and low testosterone has been shown to reduce mortality compared to that in untreated men [31, 32], although no conclusive evidence is available.

Erectile dysfunction (ED) is common in men with MetS and T2DM (up to 70% of patients). The causes of ED are multi-factorial and 30% of men with ED have co-existing testosterone-deficiency hypogonadism. Some evidence has suggested that for patients with T2DM this is only found in men with clearly reduced testosterone levels (< 8 nmol/L or 2.31 ng/mL) [33]. From a pathophysiological point of view, it has been reported that this is because ED is predominantly caused by vascular and neuropathic disease, and therefore not likely in men who do not have established vascular disease. Therefore, men presenting with ED should be screened for MetS. Likewise, patients with ED and diabetes may be offered testosterone measurement.

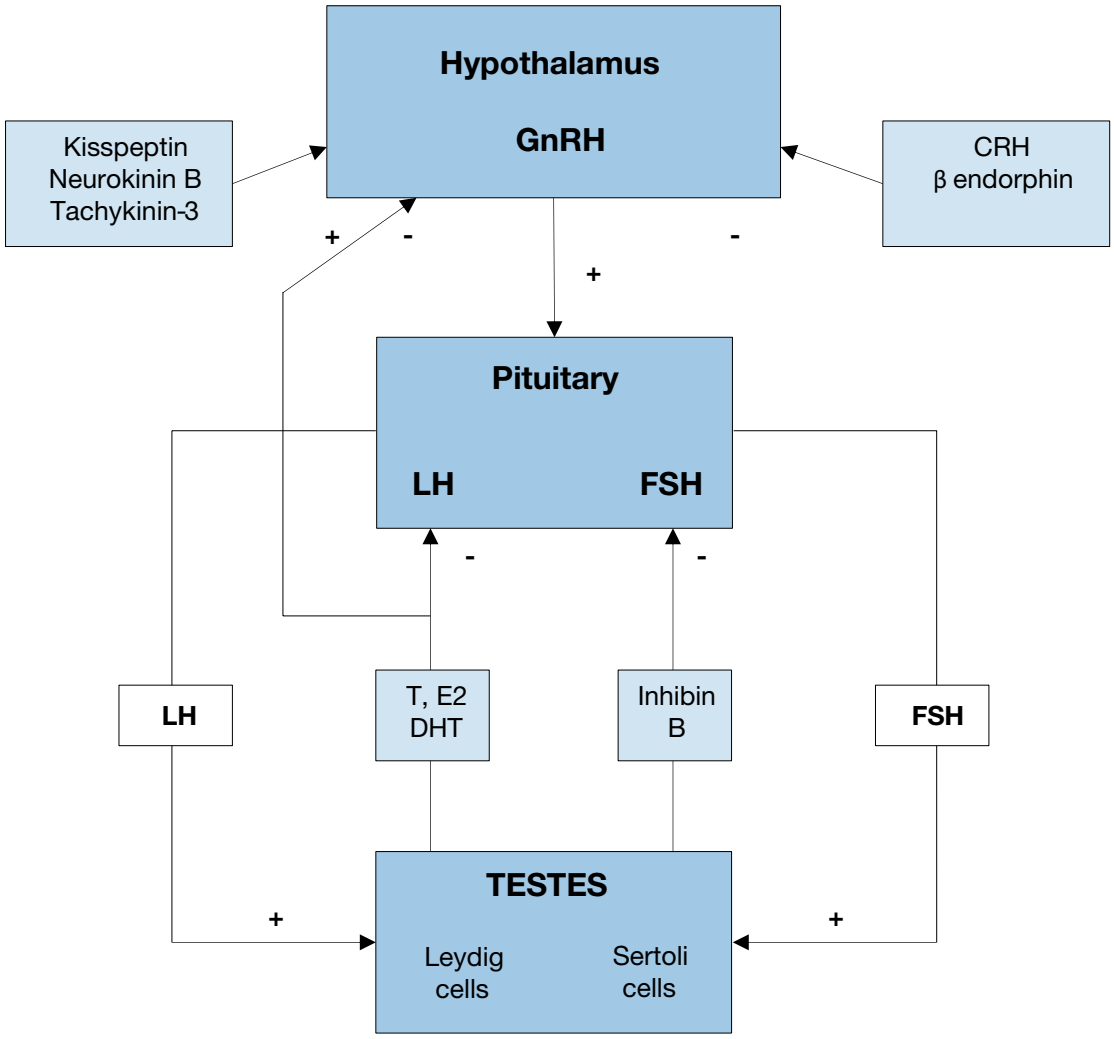
Placebo-controlled RCTs of testosterone therapy in T2DM have demonstrated improved sexual desire and satisfaction, but not erectile function [24, 33]. The presence of multiple comorbidity in this group of patients may confound the response to testosterone therapy alone. In a long-term registry study in men with T2DM, parenteral testosterone undecanoate therapy led to one third of patients entering remission from diabetes during 11 years' follow-up [34]. A large 2-year RCT of testosterone undecanoate vs. placebo showed that testosterone therapy significantly decreased progression of 999 men with low testosterone (< 14 nmol/L) from pre-diabetes to overt T2DM [30].

3.2 Physiology of testosterone production

The pituitary gland regulates testicular activity through secretion of luteinising hormone (LH), which regulates testosterone production in Leydig cells and follicle-stimulating hormone (FSH), which mainly controls sperm production in seminiferous tubules [35, 36]. The production and secretion of gonadotropins is stimulated by hypothalamic gonadotropin releasing hormone (GnRH) and inhibited by negative feedback mediated by the central action of sex steroids and inhibin B (Figure 1) [35, 36]. Gonadotropin releasing hormone is secreted in a pulsatile manner and negatively controlled by the activity of hypothalamic neurons, including corticotrophin-releasing hormone (CRH) and β endorphin neurons [35, 36]. Conversely, kisspeptin-1 (Kiss-1) neurons, neurokinin-B and tachykinin-3 are involved in GnRH stimulation. Leptin is involved in activation of Kiss-1 signalling [37]. About 25 mg of testosterone is present in the normal testes, and, on average, 5-10 mg of testosterone are secreted daily [35, 36]. The testes also produce lesser amounts of other androgens, such as androstenedione and dihydrotestosterone (DHT). A small amount of extra-gonadal testosterone is derived from

circulating weak adrenal androgen precursor dehydroepiandrosterone (DHEA), although its specific contribution to daily testosterone production is limited in men [38, 39]. In physiological terms, DHT formation accounts for 6-8% of testosterone metabolism, and the ratio of plasma testosterone/DHT is approximately 1:20 [35, 36]. Finally, testosterone and its precursor, Δ4 androstenedione, can be aromatised through P450 aromatase to other bioactive metabolites, such as oestrone (E1) and 17-β-oestradiol (E2), with a daily production of ~45 µg [35, 36]. Leydig cells, can also directly produce and release into the bloodstream small amounts of oestrogens, with a daily production rate of 5-10 µg (up to 20% of circulating oestrogens) [40].

Figure 1: Physiology of testosterone production



GnRH = gonadotropin releasing hormone; LH = luteinising hormone; FSH = follicle-stimulating hormone; T = testosterone; E2 = 17-β-estradiol; DHT = dehydroepiandrosterone; CRH = corticotrophin releasing hormone.

3.2.1 Circulation and transport of testosterone

In healthy men, 60-70% of circulating testosterone is bound to the high-affinity sex-hormone-binding globulin (SHBG), a protein produced by the liver, which prevents its bound testosterone sub-fraction from biological action. The remaining circulating testosterone binds to lower affinity, high-capacity binding proteins, (albumin, α-1 acid glycoprotein and corticosteroid-binding protein), and only 1-2% of testosterone remains non-protein bound [41]. There is a general agreement that testosterone bound to lower-affinity proteins can easily dissociate in the capillary bed of many organs, accounting for so-called 'bioavailable' testosterone [41]. It is important to recognise that several clinical conditions and ageing itself can modify SHBG levels, thus altering circulating total testosterone levels (Table 1). Therefore, if not recognised, these factors could lead to an incorrect estimation of male androgen status. Therefore, when indicated (Table 1), SHBG should be tested and free testosterone calculated.

Table 1: Main factors associated with an increase or reduction of SHBG circulating levels

SHBG increase	• Drugs: anticonvulsants, oestrogens, thyroid hormone • Hyperthyroidism • Hepatic disease • Ageing • Smoking • AIDS/HIV
SHBG decrease	• Drugs: growth hormone (GH), glucocorticoids, testosterone, anabolic androgenic steroids • Hypothyroidism • Obesity • Acromegaly [42] • Cushing's disease • Insulin resistance (MetS/T2DM) • Non-alcoholic fatty liver disease (NAFLD), • Nephrotic syndrome

*3.2.2 **Androgen receptor***

Testosterone and DHT exert their biological action through activation of a specific nuclear receptor. The androgen receptor (AR) gene is localised on the X chromosome (Xq11–12), encoded in eight exons [43]. Exon 1 includes two polymorphic trinucleotide repeat segments encoding polyglutamine (CAG) and polyglycine (GGN) tracts in the N-terminal transactivation domain of its protein. Activity of the AR is inversely associated with the length of the CAG repeat chains [43]. However, the specific role of AR CAG repeat number in relation to hypogonadal symptoms or to clinical management of testosterone deficiency remains unclear [44, 45]. A RCT has shown that a higher CAG repeat number is positively associated with a change in fasting insulin, triglyceride and diastolic blood pressure, demonstrating the more sensitive the receptor, the greater the benefit [46].

3.3 Role of testosterone in male sexual and reproductive health

*3.3.1 **Sexual development and maturation***

Testosterone production in the foetal testis starts between the eighth and ninth week of gestation after the expression of the SRY gene, which regulates organisation of the undifferentiated gonadal ridge into the testis [47]. During the first trimester, the testes drive the virilisation of internal and external genitalia through placental human chorionic gonadotropin (hCG)-stimulated androgen secretion by Leydig cells. During foetal life, testosterone mainly controls the differentiation of internal genitalia and testicular descent (regression of gubernaculum testis), whereas DHT is mainly involved in the development of the external male genitalia [48]. During puberty, reactivation of the hypothalamus–pituitary-gonadal (HPG) axis allows the development of secondary sexual characteristics, spermatogenesis maturation and, along with the contribution of other hormonal axes, completion of the adolescent growth spurt [5, 49]. Clinical models of aromatase deficiency and oestrogen receptor insensitivity have demonstrated that testosterone conversion to oestradiol is essential for epiphyseal closure and growth arrest [50].

*3.3.2 **Sexual function***

Testosterone is involved in the regulation of all steps of the male sexual response. Sexual thoughts and motivations are universally accepted as the most testosterone-dependent aspects of male sexual behaviour [20]. The European Male Aging Study (EMAS), a population-based survey including 3,369 subjects aged 40-79 years from eight European countries, showed that sexual symptoms, particularly impairment of sexual desire, ED and decreased frequency of morning erections, were the most specific symptoms associated with age-depended decline of testosterone [10]. Similar findings were reported in patients consulting for sexual dysfunctions [51]. Accordingly, several brain areas, including the amygdala, medial preoptic area, paraventricular nucleus of the hypothalamus, and peri-aqueductal grey matter express androgen receptors [51, 52]. Experimental and clinical studies have both documented that testosterone plays a crucial role in regulating penile function. In particular, testosterone controls the structural integrity necessary for penile erection, as well as several enzymatic activities within the corpus cavernosum, including a positive action on nitric oxide (NO) formation and a negative influence on the activity of the Ras homolog gene family member A/Rho-associated kinase (RhoA/ROCK) pathways [51, 53]. Testosterone is also involved in penile adrenergic response and cavernous smooth muscle cell turnover [51, 53]. Although some authors have suggested a positive role for testosterone in regulating penile phosphodiesterase 5 (PDE5) expression and activity, others have shown an inhibitory role of oestrogens on this pathway [51, 54].

More limited evidence has indicated a possible role of testosterone in regulating ejaculation, acting either at the central or peripheral level. Androgen receptors are expressed in several central spinal and supra-spinal areas involved in the control of the ejaculatory reflex [55]. Additionally, the male genital tract expresses NO-PDE5 and RhoA/ROCK pathways, which are modulated by testosterone [55].

3.4 Classification and causes of male hypogonadism

Male hypogonadism can be classified according to the origin of the underlying problem into primary, if a consequence of testicular dysfunction, or secondary, if due to a pituitary or hypothalamic dysfunction (Table 2).

Primary hypogonadism is also called hypergonadotropic hypogonadism, since the pituitary tries to compensate for testicular dysfunction by increasing central stimulation. Conversely, in secondary hypogonadism the testes are inadequately stimulated by gonadotropins, usually with inappropriately normal or reduced gonadotropin levels [5, 36]. A compensated or subclinical form of hypogonadism, characterised by normal testosterone serum levels and elevated LH production, has also been reported [56]; the clinical significance of the latter condition is unclear [56-58]. Finally, hypogonadism can also result from several conditions leading to reduced sensitivity/insensitivity to testosterone and its metabolites [5, 36] (Table 2). This classification, based on the aetiology of hypogonadism, allows clinicians to adequately select appropriate treatment. In patients with secondary hypogonadism, both fertility and testosterone normalisation can be theoretically achieved with adequate treatment whereas in primary hypogonadism only testosterone therapy can be considered, which impairs fertility due to suppression of the HGP axis [5, 36] (Table 2). However, it should also be recognised that symptoms and signs of hypogonadism can be similarly independent of the site of origin of the disease. Conversely, the age of onset of hypogonadism can influence the clinical phenotype [37]. Accordingly, when the problem starts early, such as during foetal life, clinical phenotype can span from an almost complete female phenotype (e.g., complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilisation. In the case of a pre- or peri-pubertal appearance of hypogonadism due to a milder central (isolated hypogonadotropic hypogonadism [IHH]) or a peripheral defect (such as in Klinefelter's syndrome), there might be delayed puberty with an overall eunochoid phenotype. Finally, when hypogonadism develops after puberty and especially with ageing (i.e., LOH; see below), symptoms can be mild, and often confused the with ageing process per se [5, 37].

In 2017, Grossmann and Matsumoto suggested a new classification of adult male hypogonadism, distinguishing functional versus organic hypogonadism [59]. Accordingly, organic hypogonadism is characterised by any proven pathology affecting the HPG axis and should be treated with conventional medication (i.e., gonadotropins or testosterone therapy). Conversely, functional hypogonadism is based on the absence of any recognised organic alterations in the HPG axis and should be treated first by resolving or improving the associated comorbidity. These Guidelines refer to the validated international classification of adult male hypogonadism.

A growing body of evidence has documented that although men and women show similar prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19), men usually present with worse outcomes when compared to females [60]. The possible mechanisms underlying this sex disparity are not completely understood. The demonstration that testosterone can modulate the tissue expression of angiotensin-converting enzyme 2 (ACE2) and the transcription of a transmembrane protease, serine 2 (TMPRSS2), both involved over the process of virus-cellular internalisation, suggests the possibility that androgens play a role in explaining the aforementioned sex differences [61, 62]. Interestingly, emerging data seem to suggest that low rather than elevated circulating testosterone levels are more frequently associated with worse clinical outcomes in men with COVID-19 [63-70]. This is not surprising since ACE2 is expressed in several tissues including the testis and the ACE2 receptor has been demonstrated to be present on seminiferous duct cells, as well as on spermatogonia and on Leydig and Sertoli cells, with SARS-CoV-2 potentially contributing to impaired testosterone and sperm production [71, 72]. Furthermore, it has also been suggested that the virus can result in a local intense inflammatory reaction in the testis supporting the development of a viral orchitis, eventually evolving into a vasculitis or to an autoimmune response which can contribute to testis damage and impaired testosterone production [71, 72].

Whether or not low testosterone can directly contribute to worse COVID-19 outcomes is still the objective of an intense debate. Accordingly, the possibility that low testosterone in the acute phase of the virus infection can represent as an adaptive and resilient mechanism to mitigate an external insult by turning off testosterone-dependent functions, including reproduction and/or physical and sexual activity, which are not required when the physical condition is worsening, cannot be excluded [73, 74]. Similar considerations have been proposed for late onset hypogonadism [75]. Accordingly, studies evaluating subjects in the recovery phase of COVID-19 have documented either restored [76] or persistently low testosterone levels in the majority of cases [77]. In addition, no information on the role of testosterone therapy in the acute phase of the disease is available yet. Nevertheless, male subjects recovered from SARS-CoV2 infection should be accurately followed-up to exclude any long-term andrological consequences including impairment in sperm and testosterone production.

Table 2: Classification of male hypogonadism

PRIMARY HYPOGONADISM (hypergonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*
Klinefelter syndrome	- Rare chromosomal abnormalities - XX male syndrome - 47 XYY syndrome - 48 XXYY syndrome - 21 Trisomy (Down syndrome) - Noonan syndrome - Autosomal translocations[1] - Defects of testosterone biosynthesis - CAH (testicular adrenal rest tumours) - Disorders of sex development (gonadal dysgenesis) - LHR gene mutations - Myotonic dystrophy (including type I and II) - Uncorrected cryptorchidism (including INSL3 and LGR8 mutations) - Bilateral congenital anorchia - Sickle cell disease - Adreno-leukodystrophy
Acquired disorders	
Drug-induced	*Localised problems*
- Chemotherapy agents Alkylating agents Methotrexate - Testosterone synthesis inhibitors - Ketoconazole - Aminoglutethimide - Mitotane - Metyrapon	- Bilateral surgical castration or trauma - Testicular irradiation - Orchitis (including mumps orchitis) - Autoimmune testicular failure - Testicular Torsion - Alcohol/Cirrhosis - Environmental Toxins
Systemic diseases/conditions with hypothalamus/pituitary impact	
- Chronic systemic diseases* - Chronic organ failure* - Glucocorticoid excess (Cushing syndrome)* - Aging* - HIV	- Malignancies - Lymphoma - Testis cancer - Spinal cord injury - Vasculitis - Infiltrative diseases (amyloidosis; leukaemia)
SECONDARY HYPOGONADISM (hypogonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*
- Haemochromatosis*	- Combined hormone pituitary deficiency - Idiopathic hypogonadotropic hypogonadism - (IHH) with variants: - Normosmic IHH - Kallmann syndrome - Isolated LH β gene mutations - Prader-Willi Syndrome

Acquired disorders	
Drug-induced	*Localised problems*
- Oestrogens - Testosterone or androgenic anabolic steroids - Progestogens (including cyproterone acetate) - Hyperprolactinaemia-induced drugs - Opiates - GnRH agonist or antagonist - Glucocorticoids	- Traumatic brain injury - Pituitary neoplasm (micro/macro-adenomas) - Hypothalamus tumours - Pituitary stalk diseases - Iatrogenic - Surgical hypophisectomy - Pituitary or cranial irradiation - Inflammatory and infectious diseases - Lymphocytic hypophysitis - Pituitary infections - Granulomatous lesions - Sarcoidosis - Wegener's granulomatosis - Other granulomatosis - Encephalitis - Langerhans' histiocytosis - Hyperprolactinaemia as a consequence of localised problems (hypothalamus-pituitary mass)
Systemic diseases/conditions impacting the hypothalamus/pituitary	
- Chronic systemic diseases* - Type 2 diabetes mellitus/ Metabolic Syndrome/metabolic diseases - HIV infection - Chronic organ failure - Chronic Inflammatory Arthritis - Glucocorticoid excess (Cushing syndrome)* - Eating disorders* - Endurance exercise - Acute and critical illness - Ageing*	- Spinal cord injury - Transfusion-related iron overload (β-thalassemia)
ANDROGEN RESISTANCE/DECREASED TESTOSTERONE BIOACTIVITY	
Congenital or developmental disorders	
- Aromatase deficiency - Kennedy diseases (spinal and bulbar muscular atrophy) and other extensions of CAG repeats - Partial or complete androgen insensitivity - 5α reductase type II (5αR) deficiency	

Acquired disorders	
Drug-induced	*Localised problems*
- Drug-induced AR blockage - Steroidal antiandrogen - Cyproterone acetate - Spironolactone - Non-steroidal antiandrogen - Flutamide - Bicalutamide - Nilutamide - Drug-induced 5α reductase (5αR) activity blockade - Finasteride - Dutasteride - Drug-induced ER blockade - Clomiphene - Tamoxifen - Raloxifene - Drug-induced aromatase activity blockade - Letrozole - Anastrazole - Exemestane - Increased SHBG	- Coeliac disease

** Conditions acting and central and peripheral levels resulting in either primary and secondary hypogonadism.*
[1] Different autosomal translocations can cause rare cases of hypogonadism and infertility.

3.5 Late-onset hypogonadism

Testosterone production declines with ageing. The EMAS study reported a 0.4% per annum (log hormone-age) decrease in total testosterone and a 1.3% per annum decline in free testosterone (fT) [8]. Late onset hypogonadism is the term frequently used to describe this phenomenon and the detection of hypogonadism in adulthood, in particular. Evidence has documented that several associated diseases and chronic co-morbidity can interfere with the HPG axis leading to development of primary hypogonadism or, more frequently, secondary hypogonadism in adulthood, thus significantly influencing the physiological age-dependent decline of testosterone. By combining the data from three different waves of the Massachusetts Male Aging Study (MMAS), a population-based, observational study including 1,709 men aged 40–70 years showed that associated comorbidity and obesity significantly decreased, whereas smoking tended to increase total, free and bio-available testosterone concentrations [78]. Similarly, data derived from the EMAS study confirm these findings [8, 57]. Based upon these data and other evidence, the concept of functional and organic hypogonadism has been recently introduced [59]. The diagnosis of functional hypogonadism is based on the exclusion of a classical (organic) aetiology. The main causes of functional hypogonadism are obesity, co-morbidity and ageing with the first two accounting for most cases. Inflammatory cytokines released in chronic inflammation, and adipocytokines and oestradiol in obesity, can suppress the HPG axis. The role of ageing up to age 80 years seems relatively small [59]. Considering that suppression of HPG axis activity is functional, and potentially reversible by empiric measures, such as weight loss, the need for testosterone therapy has been questioned [59].

3.5.1 Diagnostic evaluation

The phenotype of the hypogonadal patient appears independent of the aetiology causing the problem, but is more often affected by the age of onset of hypogonadism. When androgen deficiency is complete and develops during foetal life, symptoms can be dramatic, spanning from an almost complete female phenotype (complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilisation and ambiguous genitalia (micropenis, hypospadias and cryptorchidism) [5, 36]. Delay in puberty with an overall eunochoidal phenotype (scant body hair, high-pitched voice and small testes, penis and prostate) is typical of defects manifesting over the pre- or peri-pubertal period due to milder central (isolated HH) or peripheral defects (such as in Klinefelter syndrome) [5, 36]. When hypogonadism occurs in adulthood, especially functional hypogonadism, symptoms can often be mild, difficult to recognise and frequently confused with the ageing process [5, 36] or with chronic comorbidity. Several non-specific clinical features, such as fatigue, weakness, and decreased energy, as well as sexual impairment may be clinical manifestations. The EMAS study showed that a triad of sexual symptoms, including low libido, reduced spontaneous erections

and ED, are typically associated with a decrease in serum testosterone levels [10]. Conversely, psychological and physical symptoms were less informative [10].

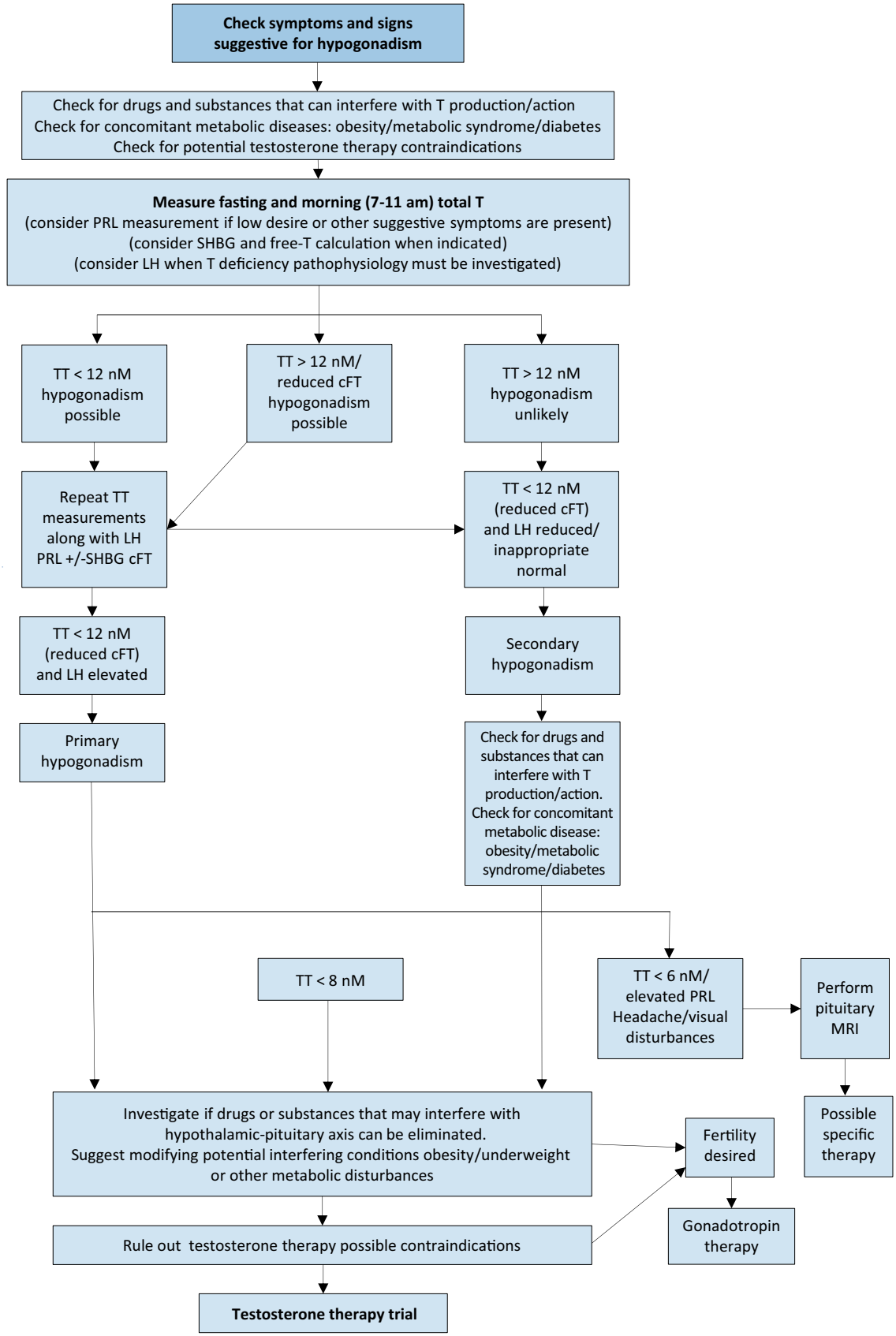
The mainstay of LOH diagnosis includes signs and symptoms consistent with hypogonadism, coupled with biochemical evidence of low morning serum total testosterone levels on two or more occasions, measured with a reliable assay. Testosterone levels show a circadian variation, which persist in ageing men [79, 80]. Likewise, testosterone levels are potentially influenced by food intake [81]; hence, serum total testosterone should be measured in fasting conditions and in the morning (between 07.00 and 11.00 hours). A confirmatory measurement should always be undertaken in the case of a primary pathological value, and certainly before starting any testosterone therapy.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) represents the gold standard and most accurate method for sex steroid evaluation; however, standardised automated platform immuno-assays for total testosterone assessment demonstrate a good correlation with LC-MS/MS [82]. Conversely, available immuno-assays are not able to provide an accurate estimation of fT; therefore, direct fT evaluation with these methods is not recommended and should be avoided [41]. Liquid chromatography-tandem mass spectrometry remains the standard method for fT determination. Alternatively, fT can be derived from specific mathematical calculations taking into account serum SHBG and albumin levels [83] (http://www.issam.ch/freetesto.htm).

Data from available meta-analyses have documented that testosterone therapy is ineffective when baseline levels are > 12 nmol/L (3.5 ng/mL). Positive outcomes are documented when testosterone levels are < 12 nmol/L, being higher in symptomatic patients with more severe forms of hypogonadism (< 8 nmol/L). Hence, 12 nmol/L should be considered as a possible threshold for starting testosterone therapy in the presence of hypogonadal symptoms [84, 85]. As reported above, clinical conditions that may interfere with SHBG levels, evaluation of fT should be considered to better estimate actual androgen levels (Figure 2). Unfortunately, despite its potential clinical value [86], no validated thresholds for fT are available from clinical studies and this represents an area of uncertainty; however, some data indicate that fT levels < 225 pmol/L (6.5 ng/dL) are associated with hypogonadal symptoms [10, 51, 87, 88].

The determination of LH must be performed along with prolactin (PRL) when pathological total testosterone levels are detected, in order to correctly define the underlying conditions and exclude possible organic causes (Figure 2). Due to its negative influence on libido, PRL can also be considered as first-line screening in patients with reduced sexual desire. In addition, pituitary magnetic resonance imaging (MRI) scanning, as well as other pituitary hormone evaluations, is required in the presence of specific symptoms such as visual disturbances, headache [89, 90] or when hyperprolactinemia is confirmed. Limited evidence suggests performing pituitary MRI also in the case of severe hypogonadism (< 6 nmol/L, 1.75 ng/mL) with inadequate gonadotropin levels (Figure 2) [89, 90].

Figure 2: Diagnostic evaluation of Late-Onset Hypogonadism


Check symptoms and signs suggestive for hypogonadism
Check for drugs and substances that can interfere with T production/action
Check for concomitant metabolic diseases: obesity/metabolic syndrome/diabetes
Check for potential testosterone therapy contraindications
Measure fasting and morning (7-11 am) total T
(consider PRL measurement if low desire or other suggestive symptoms are present)
(consider SHBG and free-T calculation when indicated)
(consider LH when T deficiency pathophysiology must be investigated)
TT < 12 nM hypogonadism possible
TT > 12 nM/ reduced cFT hypogonadism possible
TT > 12 nM hypogonadism unlikely
Repeat TT measurements along with LH PRL +/-SHBG cFT
TT < 12 nM (reduced cFT) and LH reduced/ inappropriate normal
TT < 12 nM (reduced cFT) and LH elevated
Secondary hypogonadism
Primary hypogonadism
Check for drugs and substances that can interfere with T production/action. Check for concomitant metabolic disease: obesity/metabolic syndrome/diabetes
TT < 8 nM
TT < 6 nM/ elevated PRL Headache/visual disturbances
Perform pituitary MRI
Investigate if drugs or substances that may interfere with hypothalamic-pituitary axis can be eliminated.
Suggest modifying potential interfering conditions obesity/underweight or other metabolic disturbances
Fertility desired
Possible specific therapy
Gonadotropin therapy
Rule out testosterone therapy possible contraindications
Testosterone therapy trial

TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = Magnetic resonance imaging.

3.5.2 *History taking*

Specific symptoms associated with LOH are shown in Table 3. History of surgical intervention for cryptorchidism or hypospadias must be taken into account as possible signs of congenital defects. Likewise, chronic and systemic comorbidities must be comprehensively investigated in every patient. Use of drugs that potentially interfere with the HPG axis should be ruled out (Table 2). Acute diseases are associated with development of functional hypogonadism and determination of serum total testosterone levels should be avoided in these conditions. However, as detailed above, recent data derived from SARS-CoV-2 infected patients showing worse outcomes in hypogonadal subjects suggest that the role of testosterone in the case of acute illness should be clarified [63, 91]. Several self-reported questionnaires or structural interviews have been developed for screening of hypogonadism. Although these case-history tools have demonstrated clinical utility in supporting the biochemical diagnosis of hypogonadism, or in the assessment of testosterone therapy outcomes, their specificity remains poor and they should not be used for a systematic screening of hypogonadal men [92].

Table 3: Specific symptoms associated with LOH

	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	- Reduced libido - Erectile dysfunction - Decreased spontaneous/ morning erections	- Decreased vigorous activity - Difficulty walking > 1 km - Decreased bending	- Low mood/mood deflection - Decreased motivation - Fatigue
Less specific	- Reduced frequency of sexual intercourse - Reduced frequency of masturbation - Delayed ejaculation	- Hot flushes - Decreased energy - Decreased physical strength/function/activity	- Concentration or mnemonic difficulties - Sleep disturbances

3.5.3 *Physical examination*

Since obesity is frequently associated with hypogonadism (mostly functional), the determination of body mass index (BMI) and the measurement of waist circumference are strongly recommended in all individuals. Testicular and penile size, as well the presence of sexual secondary characteristics can provide useful information regarding overall androgen status. In addition, upper segment/lower segment ratio (n.v. > 0.92) and arm-span to height ratio (n.v. < 1.0) can be useful to identify a eunochoid body shape, especially in subjects with pre-pubertal hypogonadism or delayed puberty. Finally, digital rectal examination (DRE) should be performed in all subjects to exclude prostate abnormalities before testosterone therapy (any type) or to support suspicion of hypogonadism [93].

3.5.4 *Summary of evidence and recommendations for the diagnostic evaluation of LOH*

Summary of evidence
Sexual symptoms are the most specific symptoms associated with LOH.
Diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.
Functional hypogonadism is a consequence of comorbidity/concomitant drugs, which can impair testosterone production in adulthood. The diagnosis of functional hypogonadism is a diagnosis of exclusion, after ruling out organic causes of hypogonadism.

Recommendations	Strength rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Total testosterone must be measured in the morning (07.00 and 11.00 hours) and in the fasting state, with a reliable laboratory assay.	Strong
Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy.	Strong
12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Consider sex hormone-binding globulin and free-testosterone calculation when indicated.	Strong
Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut-off to diagnose LOH.	Weak
Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between primary and secondary hypogonadism.	Strong
Consider prolactin (PRL) measurement if low sexual desire (or other suggestive signs/ symptoms) and low or low-normal testosterone is present.	Strong
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak

*3.5.5 **Recommendations for screening men with LOH***

Recommendations	Strength rating
Screen for late onset hypogonadism (LOH) (including in T2DM) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

3.6 Treatment of LOH

*3.6.1 **Indications and contraindications for treatment of LOH***

Patients with symptomatic hypogonadism (total testosterone < 12 nmol/L) without specific contraindications are suitable candidates to receive testosterone therapy (Table 4).

Absolute contraindications are untreated breast and prostate cancer (PCa). Acute cardiovascular events as well as uncontrolled or poorly controlled congestive heart failure and severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPSS) score > 19] represent other contraindications, as there is insufficient information on the long-term effects of testosterone therapy in these patients [66]. A positive family history for venous thromboembolism requires further analysis to exclude a condition of undiagnosed thrombophilia-hypofibrinolysis [94]. These patients need to be carefully counselled prior to testosterone therapy initiation. A haematocrit (HCT) > 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation to avoid any potential cardio-vascular complications. Lower baseline HTC (48-50%) should be carefully evaluated before testosterone therapy initiation, to avoid pathological increases during treatment, especially in high-risk men such as those with chronic obstructive pulmonary disease (COPD) or Obstructive Sleep Apnoea Syndrome (OSAS). Accordingly, the Framingham Heart Study showed that HCT > 48% represented a condition associated with increased risk of coronary artery disease (CAD) and mortality and was associated with cardiovascular disorders [95]. Finally, testosterone therapy suppresses gonadotropin and endogenous testosterone secretion as well as spermatogenesis. Hence, testosterone therapy is contraindicated in individuals who desire fertility [96]. Secondary hypogonadism is characterised by low or inappropriately normal gonadotropin levels; therefore, the rationale is to substitute the gonadotropin deficiency with FSH and LH analogues, if fertility is desired [97].

Table 4: Main contraindications of testosterone therapy

Absolute contraindications	Locally advanced or metastatic prostate cancer (PCa) Male breast cancer Men with an active desire to have children Haematocrit ≥ 54% Uncontrolled or poorly controlled congestive heart failure
Relative contraindication	IPSS score > 19 Baseline haematocrit 48-50% Familial history of venous thromboembolism

*3.6.2 **Testosterone therapy outcomes***

3.6.2.1 Sexual dysfunction

Sexual concerns are the main symptoms of the hypogonadal patient [5, 10, 98, 99]. A consistent body of evidence shows that testosterone therapy in hypogonadal men (total testosterone < 12 nmol/L) may have a beneficial effect on several aspects of sexual life; in contrast, there is no evidence of benefits in using testosterone therapy for treating sexual dysfunction in eugonadal men [53, 85, 100, 101]. The beneficial effect on sexual function seems to be more related to testosterone level normalisation than the specific testosterone formulations used [101, 102].

A recent meta-analysis of only placebo-controlled RCTs using the International Index of Erectile Function (IIEF) [103] as a possible tool for outcome evaluation, showed that testosterone therapy significantly improves erectile function (as measured by IIEF-Erectile Function domain score) and that patients with more severe hypogonadism (i.e., total testosterone < 8 nmol/L) are more likely to achieve better improvement than patients with milder hypogonadism (i.e., total testosterone < 12 nmol/L). Similar results were observed for sexual desire; however, the presence of metabolic comorbidity (such as diabetes and obesity) decreased the magnitude of these improvements. In particular, testosterone therapy alone resulted in a clinically effective outcome only in patients with milder ED [85]. Other sexual function parameters, such as intercourse, orgasm and overall satisfaction, were all improved compared with placebo [85]. Men with comorbidity such as diabetes usually show modest improvements in terms of sexual function after testosterone therapy and may potentially require concomitant phosphodiesterase type 5 inhibitors (PDE5Is) to improve effectiveness [5, 101]. However, the specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is not completely clear [53]. Similarly, information related to the combined use of testosterone therapy with other ED drug therapies is lacking [5, 101].

The Sexual Function Trial of the Testosterone Trials (TTrials) (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in 10 of 12 measures of sexual activities in older (≥ 65 years) hypogonadal men, particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [104]. The magnitude in improvement was shown to be proportional to the increase in serum total testosterone, fT and oestradiol levels, it was not possible to demonstrate a threshold level [105]. A study of 220 men with MetS with or without T2DM also found that sexual function improved in men who reported sexual problems with improvement in IIEF scores with specific increases in libido and sexual satisfaction [24].

3.6.2.2 Body composition and metabolic profile

Late onset hypogonadism is associated with a greater percentage fat mass and a lesser lean mass compared to testosterone-replete men [88]. The major effect of low testosterone is to increase visceral adiposity but also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [19]. Some published data have suggested that testosterone therapy reduces percentage body fat and increases lean mass [106]. Testosterone therapy has also been found to decrease waist circumference, body weight and BMI, with these effects more predominant after 12 months of treatment [106-108]. The T4DM randomised controlled trial over 2 years reported that men on testosterone therapy and lifestyle programme had a greater reduction in waist circumference, total and abdominal fat mass and an increase in total and arm muscle mass and an increased strength in the non-dominant hand compared to a lifestyle programme alone [30]. There was a trend toward reduction in body weight although this approached significance but did not reach significance. The latter result is probably compounded by the increase in muscle mass as well as the decrease in fat mass. It should be recognised, however, that the results of previous studies are mainly derived from registry and observational trials, which have important limitations due to the risk of selection bias for the non-random assignment of testosterone exposure. Accordingly, data derived from RCTs showed only an improvement of fat mass and lean mass of the same amount without any modifications in body weight [84].

3.6.2.3 Mood and cognition

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [109, 110]. However, the specific relationship between hypogonadism and the incidence of depression is still unclear [110]. Only a few placebo-controlled RCTs have investigated the role of testosterone therapy in improving depressive symptoms. Data derived from TTrials showed that testosterone therapy improved mood, and depressive symptoms as continuous measures using several instruments [104]. However, the final effect was small in magnitude. In line with these data, the largest meta-analysis of available studies, including 1,890 hypogonadal men (baseline total testosterone < 12 nmol/L or fT < 225 pmol/L) men from 27 RCTs, documented that the positive effect of testosterone therapy was particularly evident in patients with milder symptoms [111]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond with regard to symptoms of sexual dysfunction compared to men without depression [29].

Robust data on the effect of testosterone therapy on QoL are limited. Although recent meta-analyses suggest a significant effect of testosterone therapy over placebo, the magnitude is low and the heterogeneity high, therefore reducing the scientific value of the effect [102, 112].

The role of testosterone therapy in patients with cognitive impairment is even more uncertain. The TTrials evaluated the effect of testosterone therapy in 493 individuals with age-associated memory impairment in order to assess possible improvement of several aspects of cognitive function. However, the final results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [104].

3.6.2.4 Bone

Evidence suggests that bone mineralisation requires circulating sex steroids within the normal range [113]. The possible association between mild hypogonadism and osteopenia/osteoporosis is weak, whereas severe hypogonadism (total testosterone < 3.5 nM) is frequently associated with bone loss and osteoporosis, independent of patient age [113]. Two independent meta-analyses showed a positive effect of testosterone therapy on bone mineral density (BMD), with the highest effect at the lumber level [114, 115]. Similarly, data derived from TTrials and the T4DM studies confirmed that testosterone therapy increased BMD in hypogonadal ageing men. The TTrial found increased BMD in trabecular bone at the lumbar level [104], whereas the T4DM study reported greater increases in cortical bone [116]. Changes in hip and spine BMD were similar in both studies. However, available data are insufficient to determine the effect of testosterone therapy alone on the risk of fractures [113]. The use of testosterone therapy as an adjunct to anti-resorptive treatment in hypogonadal patients at high risk of fractures has not been established. Therefore, anti-resorptive therapy must be the first-choice treatment in hypogonadal men at high risk for bone fractures. The combination of anti-resorptive treatment and testosterone therapy should be offered only in conjunction with hypogonadism-related symptoms.

3.6.2.5 Vitality and physical strength

The role of testosterone in stimulating muscle growth and strength is well established. Accordingly, androgenic-anabolic steroids (AAS) have been used as performance-enhancing agents to increase physical performance in competitive sport [117]. In this regard, testosterone therapy in hypogonadal men has been shown to increase muscle mass and reduce fat mass, with limited effects on final weight [84]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. The National Health and Nutrition Examination Survey 1999-2004 [118] was unable to detect any association between overall circulating testosterone levels and the amount of physical activity. However, among non-obese men, those in the highest physical activity tertile were significantly less likely to have low or low-normal testosterone than those in the lowest tertile. Data from TTrials indicated that testosterone therapy did not substantially increase the fraction of men whose 6-minute walking distance increased > 50 m or the absolute increase in the distance walked by those enrolled in the physical function trial [104]. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these two parameters was reported [104]. Similar data were derived from the Vitality Trial [104].

3.6.2.6 Summary of evidence and recommendations for testosterone therapy outcome

Summary of evidence
Testosterone therapy can improve milder forms of ED and libido in hypogonadal men.
Testosterone therapy can improve other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.
Testosterone therapy can similarly increase lean mass, reduce fat mass, and improves insulin resistance.
Testosterone therapy can improve weight, waist circumference and lipid profile, but findings are not unique.
Testosterone therapy can improve milder depressive symptoms in hypogonadal men.
Testosterone therapy can improve bone mineral density, but information related to fracture risk is lacking.

Recommendations	Strength rating
The use of testosterone therapy in eugonadal men is not indicated.	Strong
Use testosterone therapy as first-line treatment in patients with symptomatic hypogonadism and mild erectile dysfunction (ED).	Strong
Use combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong

3.6.3 ***Choice of treatment***

3.6.3.1 Lifestyle factors

As reported above, functional hypogonadism is frequently associated with obesity and metabolic disorders [119]. Therefore, weight loss and lifestyle changes should be the first approach for all overweight and obese men with hypogonadism. A previous meta-analysis documented that a low-calorie diet is able to revert obesity-associated secondary hypogonadism by increasing total testosterone and fT, reducing oestrogens and restoring normal gonadotropin circulating levels [120]. This was confirmed in a recent updated meta-analysis showing that the increase in testosterone is significantly associated with weight reduction [121]. Similar results can be obtained through physical activity, which is associated with the duration of scheduled exercise and weight loss obtained [121]. However, it should be recognised that the increase in testosterone levels observed after a low-calorie diet and physical activity is small (1-2 nmol) [120, 121]. It should also be recognised that 60-86% of weight lost is regained after 3 years and 75-121% after 5 years [122]. A greater testosterone increase can be achieved through bariatric surgery, which results in an average increase of about 10 nmol/L depending on the degree of weight loss [121]. Lifestyle changes represent an essential part of the management of obesity; however, some evidence suggests that when compared to lifestyle modifications alone, testosterone therapy-treated obese men benefit most from relief of their symptoms associated with testosterone deficiency, whereas those not treated did not benefit [97]. There is limited evidence to suggest that combination of life-style interventions and testosterone therapy in symptomatic hypogonadal men might result in better outcomes [88]. The T4DM study as described above has demonstrated that over 2-years testosterone therapy with lifestyle intervention was superior to lifestyle intervention alone in reducing waist circumference and total and abdominal fat content. There was no significant reduction in body weight when compared to lifestyle intervention alone [30].

3.6.3.2 Medical preparations

Several testosterone formulations are available (Table 5). Direct comparisons among different testosterone products are still lacking. Candidates for testosterone therapy should be adequately informed about the possible risks and benefits of all available testosterone preparations. The final choice should be based on the clinical situation, testosterone formulation availability, and patient needs and expectations [123].

3.6.3.2.1 Oral formulations

The esterification of testosterone with a long-chain fatty acid (testosterone undecanoate; TU) enables testosterone to be absorbed by the intestine through the lymphatic system, by-passing liver metabolism. This formulation has been available in oleic acid since the 1970s, and it has been recently reformulated in a mixture of castor oil and propylene glycol laureate (TU caps), to allow the drug to be maintained at room temperature without degradation [123]. The main limitation is related to the poor bioavailability, which is strongly dependent

on dietary fat content [123]. Recently, the US Food and Drug Administration (FDA) approved a new formulation of oral TU incorporating a liquid-filled hard capsule drug delivery system and a higher amount (225 mg) of the compound, which improves oral availability (https://www.fda.gov/media/110187/download). In an open label study of approximately 4 months' duration (NCT02722278), 145 (87%) of 166 hypogonadal men enrolled who received the TU caps formulation had mean total testosterone concentration within the normal eugonadal range at the end of treatment (https://www.fda.gov/media/110187/download). However, the TU caps compound is not available in Europe.

Mesterolone is a 5α-DHT derivate available for oral administration. Along with DHT, mesterolone cannot be converted to oestrogens and can only be used for a limited period and specific indications, such as the presence of painful gynaecomastia. However, the lack of a full spectrum of testosterone bioactivity strongly limits its long-term use [123].

3.6.3.2.2 Parenteral formulations

Injectable testosterone preparations can be classified according to their half-lives (Table 5). Testosterone propionate is a short-term ester formulation requiring multiple fractionated doses (usually 50 mg, every 2-3 days), thus representing a major limitation for its use [123]. Cypionate and enanthate-T esters are short-term formulations, requiring administration every 2-4 weeks. A formulation containing mixed testosterone esters (TU, isocaproate, phenyl propionate, propionate - Sustanon®) which allows some benefit of a smoother release of testosterone into the circulation is available in some countries. The use of these older formulations is associated with wide fluctuations in plasma testosterone concentrations and is often reported as unpleasant by patients and potentially resulting in adverse effects, such as polycythaemia [123, 124]. A longer-lasting TU injectable formulation is widely available [123]; which has a good safety/benefit profile allowing the maintenance of normal stable testosterone levels at a dose of 1,000 mg initially every 12 weeks, following a 6-week loading dose, but can be adjusted to a frequency of 10-14 weeks dependent on the trough (pre-injection level) after 3-5 injections to maintain levels in the therapeutic range (usually > 12 and < 18 nmol/L) [123, 125].

3.6.3.2.3 Transdermal testosterone preparations

Among the available transdermal formulations, testosterone gels represent the most frequently used preparations. The gel is quickly absorbed by the stratum corneum, creating a reservoir within the subcutaneous tissues from where testosterone is continuously delivered for 24 hours, after a single daily application. These formulations have been shown to normalise serum testosterone levels with an excellent safety profile [123]. The introduction of specific devices and skin enhancers has resulted in better skin penetration of the drugs, thus reducing potential adverse effects. Local skin adverse effects are limited when compared to those with traditional testosterone patches, but they potentially allow transference of testosterone during close contact with the skin surface. The risk can be reduced by wearing clothing or by applying the gel on skin surfaces not usually touched (e.g., the inner thigh surface) [123]. To reduce the total amount of gel applied and residual quantities remaining on the skin, new formulations of testosterone gel have been introduced with a testosterone concentration of 1.62-2% [123]. Another transdermal testosterone formulation includes a topical, alcohol-based testosterone (2%) solution, which must be applied to the underarm once daily, using a metered dose applicator [123]. This testosterone formulation is not available in Europe. Testosterone levels should be monitored to optimise the testosterone dose. Blood collection is best taken at 2-4 hours after gel application to use the peak level of testosterone absorbed as a reference for adequate therapeutic levels. Levels of testosterone after application can vary and a repeat measurement may be indicated especially as sometimes, inadvertently, the skin over the vene-puncture site can be contaminated by the gel, leading to falsely elevated results.

In some European countries, DHT is available as a hydroalcoholic 2.5% gel. It is rapidly absorbed, reaching a steady state in 2-3 days. Similar to that reported for mesterolone, DHT is not aromatised but can be useful for treating particular conditions, such as gynaecomastia and microphallus [123].

3.6.3.2.4 Transmucosal formulations

3.6.3.2.4.1 Transbuccal testosterone preparations

A testosterone buccal system is still available in several countries. It consists on a sustained-release muco-adhesive buccal-testosterone-tablet requiring twice-daily application to the upper gums. The tablet does not dissolve completely in the mouth and must be removed after 12 hours. This formulation has been proven to restore testosterone levels within the physiological range with minimal or transient local problems, including gum oedema, blistering and gingivitis [123].

3.6.3.2.4.2 Transnasal testosterone preparations

A gel for intranasal administration is available in some countries, including the USA and Canada. It requires

administration two or three times daily using a specific metered-dose pump. The application is rapid, non-invasive, convenient, and avoids secondary transference observed with other topical products [123].

3.6.3.2.5 Subdermal depots

The implantation of testosterone pellets, available in the USA, UK and Australia, represents the longest available testosterone formulation lasting from 4-7 months. However, the procedure is invasive and may be unattractive to patients [123].

3.6.3.2.6 Anti-oestrogens

Anti-oestrogens, including selective oestrogen receptor (ER) modulators (SERMs) and aromatase inhibitors (AI) have been suggested as off-label treatments to restore testosterone levels and fertility in men with functional secondary hypogonadism or idiopathic infertility. They work by preventing down-regulation of the HPG axis by oestrogens and, for this reason are particularly useful in men with obesity and metabolic disorders [121]. In the latter case, the hypothesis is that the excess of adipose tissue leads to increased aromatase activity and oestrogens levels resulting in impairment of the HPG [119]. Due to their putative mechanism of action, they require an intact HPG axis and cannot work in primary hypogonadism or secondary hypogonadism due to organic damage of the HPG axis. Both types of SERMs, which bind ERs with an agonist or antagonist effect depending upon the target tissue, and AIs, which prevent androgens from being converted into oestrogens by aromatase, have been used in clinical practice [123]. The evidence published so far is poor; all these products are off-label treatments and SERMs, due to their agonistic effect on venous vessels, could predispose men to the development of venous thromboembolism [123]. In this context patients should be warned of the potential increased risk of venous thromboembolism, although data are lacking. Long-term use of these agents can lead to reduced bone density and development of osteoporosis, potentially increasing fracture risk.

3.6.3.2.7 Gonadotropins

Considering the aforementioned limitations regarding the use of anti-oestrogens, gonadotropin therapy should be considered the standard in men with secondary hypogonadism who desire paternity (Table 5) [123]. The treatment is based on the use of human chorionic gonadotropin (hCG), purified from the urine of pregnant women. The most expensive recombinant hCG (rhCG) and LH (rLH) formulations do not offer clinical advantages [123]. According to a meta-analysis of the available evidence, hCG should be administered with FSH as combined therapy results in better outcomes. Similar to recombinant hCG, recombinant FSH (rFSH) does not seem to offer any advantages compared to urinary-derived preparations [125]. More details on the use of gonadotropins are provided in Section 10.

Table 5: Available preparations for hypogonadism treatment

Formulation	Chemical structure	t 1/2	Standard dosage	Advantages	Disadvantages
GONADOTROPINS					
Human chorionic gonadotrophin (HCG)					
Extractive	HCG purified from the urine of pregnant women	NA	1,000-2,000 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant HCG	NA	No data in men	NA	
Luteotropic hormone (LH)					
Recombinant	Human recombinant LH	NA	No data in men	NA	
Follicle-stimulating hormone (FSH)					
Extractive	FSH purified from urine of pregnant women	NA	75-150 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant FSH	NA	75-150 IU 3 times/week		Multiple weekly administration

TESTOSTERONE PREPARATIONS					
Oral					
Testosterone undecanoate	17-α-hydroxylester	4 hours	120-240 mg 2-3 times daily	- Reduction of liver involvement - Oral convenience - Modifiable dosage	- Unpredictable absorption depending on dietary fat content - Must be taken with meals
Mesterolone	1α-methyl-4, 5α-dihydro-testosterone	12 hours	50-100 mg 2-3 times daily	- Oral convenience - Modifiable dosage - Useful in gynaecomastia	- Not aromatisable
Parental					
Testosterone enanthate	17-α-hydroxylester	4-5 days	250 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone cypionate	17-α-hydroxylester	8 days	200 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone propionate	17-α-hydroxylester	20 hours	100 mg every 2 days	- Low cost - Very short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone ester mixture Propionate (30mg) Phenylpropionate (60 mg) Isocaproate (60 mg) Decanoate (100 mg)	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4-5 days	250 mg every 3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone undecanoate in castor oil	17-α-hydroxylester	34 days	1,000 mg every 10-14 weeks *750 mg every 10 weeks	- Steady-state testosterone level without fluctuation - Long-lasting - Less frequent administration	- Pain at injection site - Long-acting preparation not allowing rapid drug withdrawal in case of adverse effects
Surgical implants	Native testosterone	--	4-6 200 mg implants lasting up to 6 months	- Long duration and constant serum testosterone level	- Placement is invasive - Risk of extrusion and site infections

TRANSDERMAL					
Testosterone patches	Native testosterone	10 hours	50-100 mg/ day	Steady-state testosterone level without fluctuation	- Skin irritation - Daily administration
Testosterone gel 1-2%	Native testosterone	6 hours	50-100 mg/ day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Underarm testosterone (testosterone solution 2%)	Native testosterone	NA	60-120 mg/ day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Dihydro-testosterone gel 2.5%	Native dihydro-testosterone	NA	34-70 mg/day	- Steady-state testosterone level without fluctuation - Useful in gynaecomastia	- Possible transfer during intimate contact - Daily administration - Not aromatisable
TRANSMUCOSAL					
Testosterone buccal system	Native testosterone	12 hours	60 mg 3 times daily	Steady-state testosterone level without fluctuation	- Possible oral irritation - Twice-daily dosing - Unpleasant taste
Testosterone nasal	Native testosterone	6 hours	33 mg 3 times daily	Steady-state testosterone level without fluctuation	- Nasal irritation - Multiple daily administration

NA = not applicable.

3.6.3.3 Summary of evidence and recommendations for choice of treatment for LOH

Summary of evidence
Weight loss obtained through a low-calorie diet and regular physical activity result in a small improvement in testosterone levels.
Testosterone gels and long-acting injectable TU represent T preparations with the best safety profile.
Gonadotropins treatment can be used to restore fertility in men with secondary hypogonadism.

Recommendations	**Strength rating**
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs that can impair testosterone production; treat co-morbidity before starting testosterone therapy.	Weak
Fully inform patients about expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, only with fully informed patients.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse effects.	Weak

3.7 Safety and follow-up in hypogonadism management

3.7.1 Hypogonadism and fertility issues

The aim of pharmacological management of hypogonadism is to increase testosterone levels. The first choice is to administer exogenous testosterone. However, while exogenous testosterone has a beneficial effect on

the clinical symptoms of hypogonadism, it inhibits gonadotropin secretion by the pituitary gland, resulting in impaired spermatogenesis and sperm cell maturation [126]. Therefore, testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment [96]. When secondary hypogonadism is present, gonadotropin therapy may maintain normal testosterone levels and restore sperm production [5].

3.7.2 ***Male breast cancer***

In vitro and *in vivo* studies have clearly documented that breast cancer growth is significantly influenced by testosterone and/or by its conversion to E2 through different mechanisms and pathways [127]. Accordingly, the use of SERMs still represents an important therapeutic option in the management of this cancer [127]. No information is available on the role of testosterone therapy in patients successfully treated for male breast cancer; therefore, treated and active male breast cancer should be recognised as absolute contraindications for testosterone therapy.

3.7.3 ***Lower urinary tract symptoms/benign prostatic hyperplasia***

Based on the assumption that prostate growth is dependent on the presence of androgens, historically testosterone therapy historically has raised some concerns regarding the possibility of aggravating LUTS in patients affected by benign prostatic hyperplasia (BPH) associated with prostate enlargement [93, 128]. However, pre-clinical and clinical data have indicated that low rather than high androgen levels may decrease bladder capacity, alter tissue histology and decrease the ratio of smooth muscle to connective tissue, thus impairing urinary dynamics [93, 128].

A trial of 60 patients undergoing testosterone therapy for 6 months showed no significant differences in post-voidal residual urine and prostate volume, while storage symptoms as measured by IPSS significantly improved, despite an increase in prostate-specific antigen (PSA) level. A larger pre-treatment prostate volume was a predictive factor of improvement in LUTS [129]. A long-term study of 428 men undergoing testosterone therapy for 8 years demonstrated significant improvements in IPSS, no changes max flow rate (Q_{max}) and residual urine volume, but also a significant increase in prostate volume [130]. Similar data from the Registry of Hypogonadism in Men (RHYME), including 999 patients with a follow-up of 3 years, did not document any difference in PSA levels or total IPSS in men undergoing testosterone therapy, compared to untreated patients [131]. Similar results were reported in an Italian registry (SIAMO-NOI), collecting data from 432 hypogonadal men from 15 centres [132]. Meta-analyses have not found significant changes in LUTS between patients treated with testosterone or placebo [133-139]. According to the most recent literature, there are no grounds to discourage testosterone therapy in hypogonadal patients with BPH/LUTS and there is evidence of limited benefit from androgen administration. The only concern is related to patients with severe LUTS (IPSS > 19), as they are usually excluded from RCTs, therefore limiting the long-term safety data of testosterone therapy in this specific setting [93].

3.7.4 ***Prostate cancer (PCa)***

A considerable number of observational studies have failed to demonstrate any association between circulating higher testosterone levels and PCa [140]. In contrast, studies investigating the relationship between low levels of testosterone and risk of PCa have found that men with very low levels of fT have a reduced risk of developing low-to-intermediate-grade PCa, but have a non-significantly increased chance of developing high-grade PCa [140]. This peculiar pattern was also reported in trials such as the Health Professionals Follow-up Study, the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), with varying magnitudes of significance [141].

The most recent meta-analysis, including 27 placebo-controlled, RCTs, found no evidence of increased PSA levels following testosterone therapy for one year. When considering 11 studies reporting on the occurrence of PCa, the meta-analysis found no evidence of increased risk of PCa. However, a 1-year follow-up may be considered too short to draw firm conclusions on the risks of developing PCa. Furthermore, the analysis was restricted to studies with > 1-year follow-up, but no significant changes in PSA levels nor increased risk of PCa were found [134]. After 5-years' median follow-up in three independent registry studies with > 1,000 patients undergoing testosterone therapy, PCa occurrence remained at all times below the reported incidence rate in the general population [142]. Similar results were reported by a more recent large observational study including 10,311 men treated with testosterone therapy and 28,029 controls with a median follow-up of 5.3 years [143]. The same study, also showed that the risk of PCa was decreased for men in the highest tertile of testosterone therapy cumulative dose exposure as compared with controls [143].

With regards to PCa survivors, safety in terms of the risk of recurrence and progression has not yet been established. Limited data are available in the literature, with most case series not providing sufficient data to draw definitive conclusions (e.g., insufficient follow-up, small samples, lack of control arms, heterogeneity in study population and treatment regimen, etc.) [144]. More recently, a meta-analysis derived from 13 studies

including 608 patients, of whom 109 had a history of high-risk PCa, with follow-up of 1-189.3 months [145], suggested that testosterone therapy did not increase the risk of biochemical recurrence, but the available evidence is poor, limiting data interpretation [145]. Similar considerations can be derived from another, larger meta-analysis of 21 studies [146]. It is important to recognise that most of the studies analysed included low-risk patients with Gleason score < 8 [145].

In conclusion, recent literature does not support an increased risk of PCa in hypogonadal men undergoing testosterone therapy. Although it is mandatory to avoid testosterone administration in men with advanced PCa, insufficient long-term prospective data on the safety of androgen administration in PCa survivors [146], without recurrence should prompt caution in choosing to treat symptomatic hypogonadal men in this setting. Specifically, patients should be fully counselled that the long-term effects of testosterone therapy in this setting are still unknown and requires further investigation. If an occult PCa is not detected before initiation of testosterone therapy, treatment may unmask the cancer detected by an early rise in PSA over 6-9 months of therapy. Due to the lack of strong evidence-based data on safety, the possible use of testosterone therapy in symptomatic hypogonadal men previously treated for PCa should be fully discussed with patients and limited to low-risk individuals.

*3.7.5 **Cardiovascular Disease***

Evidence suggests that hypogonadal men have an increased risk of CVD [75, 147]. Whether or not LOH is a cause or a consequence of atherosclerosis has not been clearly determined. Late-onset hypogonadism is associated with CV risk factors, including central obesity, insulin resistance and hyperglycaemia, dyslipidaemia (elevated total cholesterol, LDL-cholesterol, triglycerides and low HDL-cholesterol), pro-thrombotic tendency and chronic inflammatory state [147]. Atherosclerosis is a chronic inflammatory disease, that releases pro-inflammatory cytokines into the circulation, which are known to suppress testosterone release from the HPG axis. Evidence from RCTs of testosterone therapy in men with MetS and/or T2DM demonstrates some benefit in CV risk, including reduced central adiposity, insulin resistance, total cholesterol and LDL-cholesterol and suppression of circulating cytokines [14, 23-25, 29, 147]. However, due to the equivocal nature of these studies, testosterone therapy cannot be recommended for indications outside the specific symptoms.

Published data show that LOH is associated with an increase in all-cause and CVD-related mortality [12, 148-151]. These studies are supported by a meta-analysis that concluded that hypogonadism is a risk factor for cardiovascular morbidity [138] and mortality [152]. Importantly, men with low testosterone when compared to eugonadal men with angiographically proven coronary disease have twice the risk of earlier death [147]. Longitudinal population studies have reported that men with testosterone in the upper quartile of the normal range have a reduced number of CV events compared to men with testosterone in the lower three quartiles [148]. Androgen deprivation therapy for PCa is linked to an increased risk of CVD and sudden death [153]. Conversely, two long-term epidemiological studies have reported reduced CV events in men with high normal serum testosterone levels [154, 155]. Erectile dysfunction is independently associated with CVD and may be the first clinical presentation in men with atherosclerosis.

The knowledge that men with hypogonadism and/or ED may have underlying CVD should prompt individual assessment of their CV risk profile. Individual risk factors (e.g., lifestyle, diet, exercise, smoking, hypertension, diabetes and dyslipidaemia) should be assessed and treated in men with pre-existing CVD and in patients receiving androgen deprivation therapy. Cardiovascular risk reduction can be managed by primary care clinicians, but patients should be appropriately counselled by clinicians active in prescribing testosterone therapy [98]. If appropriate, they could be referred to cardiologists for risk stratification and treatment of co-morbidity.

No RCTs have provided a clear answer on whether testosterone therapy affects CV outcomes. The TTrial (n=790) in older men [156], the TIMES2 (n=220) [24], the BLAST studies in men with MetS and T2DM and the pre-frail and frail study in elderly men - all of 1-year duration and the T4DM 2-year study - did not reveal any increase in Major Adverse Cardiovascular Events (MACE) [24, 27, 30, 156, 157]. In this context, MACE is defined as the composite of CV death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. Randomised controlled trials between 3 and 12 months in men with known heart disease treated with testosterone have not found an increase in MACE, but have reported improvement in cardiac ischaemia, angina and functional exercise capacity [158-160]. A large cohort study (n=20, 4,857 men) found that neither transdermal gels or intramuscular testosterone was associated with an increased risk of composite cardiovascular outcome in men with or without prevalent cardiovascular disease (mean follow up 4.3 years) [161]. The European Medicines Agency (EMA) has stated that 'The Co-ordination Group for Mutual recognition and Decentralisation Procedures-Human (CMDh), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone in men who lack the hormone (a condition known as hypogonadism). However, the product

information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these drugs [162].

As a whole, as for MACE, current available data from interventional studies suggest that there is no increased risk with up to 3 years of testosterone therapy [163-166]. The weight of the currently published evidence has reported that testosterone therapy in men with diagnosed hypogonadism has neutral or beneficial actions on MACE in patients with normalised testosterone levels. The findings could be considered sufficiently reliable for a 3-year course of testosterone therapy, after which no available study can exclude further or long-term CV events [167, 168].

3.7.5.1 Cardiac Failure

Testosterone treatment is contraindicated in men with severe chronic cardiac failure because fluid retention may lead to exacerbation of the condition. Some studies including one of 12 months' duration have shown that men with moderate chronic cardiac failure may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [159, 169, 170]. If a decision is made to treat hypogonadism in men with chronic cardiac failure, it is essential that the patient is followed up carefully with clinical assessment and both testosterone and haematocrit measurements on a regular basis. An interesting observation is that untreated hypogonadism increased the re-admission and mortality rate in men with heart failure [171].

*3.7.6 **Erythrocytosis***

An elevated haematocrit is the most common adverse effect of testosterone therapy. Stimulation of erythropoiesis is a normal biological action that enhances delivery of oxygen to testosterone-sensitive tissues (e.g., striated, smooth and cardiac muscle). Any elevation above the normal range for haematocrit usually becomes evident between 3 and 12 months after testosterone therapy initiation. However, polycythaemia can also occur after any subsequent increase in testosterone dose, switching from topical to parenteral administration and, development of co-morbidity, which can be linked to an increase in haematocrit (e.g., respiratory or haematological diseases).

There is no evidence that an increase of haematocrit up to and including 54% causes any adverse effects. If the haematocrit exceeds 54% there is a testosterone independent, but weak associated rise in CV events and mortality [95, 172-174]. Any relationship is complex as these studies were based on patients with any cause of secondary polycythaemia, which included smoking and respiratory diseases. There have been no specific studies in men with only testosterone-induced erythrocytosis.

Three large studies have not shown any evidence that testosterone therapy is associated with an increased risk of venous thromboembolism [175, 176]. However, one study showed that an increased risk peaked at 6 months after initiation of testosterone therapy, then declined over the subsequent period [177]. No study reported whether there was monitoring of haematocrit, testosterone and/or E2 levels. High endogenous testosterone or E2 levels are not associated with a greater risk of venous thromboembolism [178]. In one study venous thromboembolism was reported in 42 cases and 40 of these had diagnosis of an underlying thrombophilia (including factor V Leiden deficiency, prothrombin mutations and homocysteinuria) [179]. In a RCT of testosterone therapy in men with chronic stable angina there were no adverse effects on coagulation, by assessment of tissue plasminogen activator or plasminogen activator inhibitor-1 enzyme activity or fibrinogen levels [180]. A meta-analysis of RCTs of testosterone therapy reported that venous thromboembolism was frequently related to underlying undiagnosed thrombophilia-hypofibrinolysis disorders [94]. However, another meta-analysis and systematic review of randomised controlled trials found that testosterone replacement therapy was not associated with an increased risk of venous thromboembolism [181]. With testosterone therapy an elevated haematocrit is more likely to occur if the baseline level is toward the upper limit of normal prior to initiation. Added risks for raised haematocrit on testosterone therapy include smoking or respiratory conditions at baseline. Higher haematocrit is more common with parenteral rather than topical formulations. In men with pre-existing CVD extra caution is advised with a definitive diagnosis of hypogonadism before initiating testosterone therapy and monitoring of testosterone as well as haematocrit during treatment.

Elevated haematocrit in the absence of co-morbidity or acute CV or venous thromboembolism can be managed by a reduction in testosterone dose, change in formulation or if the elevated haematocrit is very high by venesection (500 mL), even repeated if necessary, with usually no need to stop the testosterone therapy.

*3.7.7 **Obstructive Sleep Apnoea***

There is no evidence that testosterone therapy can result in onset or worsening of sleep apnoea. Combined therapy with Continuous Positive Airway Pressure (CPAP) and testosterone gel was more effective than CPAP

alone in the treatment of obstructive sleep apnoea [182]. In one RCT, testosterone therapy in men with severe sleep apnoea reported a reduction in oxygen saturation index and nocturnal hypoxaemia after 7 weeks of therapy compared to placebo, but this change was not evident after 18 weeks' treatment and there was no association with baseline testosterone levels [183].

*3.7.8 **Follow-up***

Testosterone therapy alleviates symptoms and signs of hypogonadism in men in a specific time-dependent manner. The TTrials clearly showed that testosterone therapy improved sexual symptoms as early as 3 months after initiation [104]. Similar results have been derived from meta-analyses [53, 94]. Hence, the first evaluation should be planned after 3 months of treatment. Further evaluation may be scheduled at 6 months or 12 months, according to patient characteristics, as well as results of biochemical testing (see below). Table 6 summarises the clinical and biochemical parameters that should be monitored during testosterone therapy.

Trials were designed to maintain the serum testosterone concentration within the normal range for young men (280–873 ng/dL or 9.6-30 nmol/L) [104]. This approach resulted in a good benefit/risk ratio. A similar approach could be considered during follow-up. The correct timing for evaluation of testosterone levels varies according to the type of preparation used (Table 5). Testosterone is involved in the regulation of erythropoiesis [124] and prostate growth [93], hence evaluation of PSA and haematocrit should be mandatory before and during testosterone therapy. However, it is important to recognise that the risk of PCa in men aged < 40 years is low. Similarly, the mortality risk for PCa in men aged > 70 years is not been considered high enough to warrant monitoring in the general population [184]. Hence, any screening for PCa through determination of PSA and DRE in men aged < 40 or > 70 years during testosterone therapy should be discussed with the patients.

Baseline and, at least, annually glyco-metabolic profile evaluation may be a reasonable consideration, particularly in the management of functional hypogonadism. Testosterone therapy may be beneficial for hypogonadal men with low or moderate fracture risk [113]; therefore, dual energy X-ray absorptiometry (DEXA) bone scan may also be considered at baseline and 18-24 months following testosterone therapy, particularly in patients with more severe hypogonadism [113].

Digital rectal examination may detect prostate abnormalities that can be present even in men with normal PSA values. Hence, DRE is mandatory in all men at baseline and during testosterone therapy.

The decision to stop testosterone therapy or to perform prostate biopsy due to PSA increase or prostate abnormalities should be based on local PCa guidelines. There is a large consensus that any increase of haematocrit > 54% during testosterone therapy requires therapy withdrawal and phlebotomy to avoid potential adverse effects including venous-thromboembolism and CVD, especially in high-risk individuals. In patients with lower risk of relevant clinical sequelae, the situation can be alternatively managed by reducing testosterone dose and switching formulation along with venesection. A positive family history of venous-thromboembolism should be carefully investigated and the patient counselled with regard to testosterone therapy to avoid/prevent thrombophilia-hypofibrinolysis [94]. Finally, caution should be exercised in men with pre-existing CVD or at higher risk of CVD.

Table 6: Clinical and biochemical parameters to be checked during testosterone therapy

Parameters	**Year 1 of treatment**			**After year 1 of treatment**	
	Baseline	**3 months**	**6/12 months**	**Annually**	**18-24 months**
Clinical					
Symptoms	X	X	X	X	
Body Mass Index					
Waist circumference	X	X	X	X	
Digital rectal examination	X	X	X	X	
Blood pressure	X	X	X	X	
Biochemistry					
PSA (ng/mL)	X	X	X	X	
Haematocrit (%)	X	X	X	X	
Testosterone	X	X	X	X	
Lipid and glycaemic profile	X		X	X	
Instrumental					
DEXA	X				X

3.7.9 *Summary of evidence and recommendations on risk factors in testosterone treatment*

Summary of evidence
Testosterone therapy is contraindicated in men with secondary hypogonadism who desire fertility.
Testosterone therapy is contraindicated in men with active prostate cancer or breast cancer.
Testosterone therapy does not increase the risk of prostate cancer, but long-term prospective follow-up data are required to validate this statement.
The effect of testosterone therapy in men with severe lower-urinary tract symptoms is limited, as these patients are usually excluded from RCTs.
There is no substantive evidence that testosterone therapy, when replaced to normal levels, results in the development of major adverse cardiovascular events.
There is no evidence of a relationship between testosterone therapy and mild, moderate or CPAP-treated severe sleep apnoea.

Recommendations	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., pre-operative PSA < 10 ng/mL; Gleason score < 7 [International Society for Urological Pathology grade 1]; cT1-2a)* and treatment should start after at least 1 year follow-up with PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before starting testosterone therapy.	Strong
Monitor testosterone, haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

**As for EAU risk groups for biochemical recurrence of localised or locally advanced prostate cancer (see EAU Prostate Cancer Guidelines, 2022)*

4. EPIDEMIOLOGY AND PREVALENCE OF SEXUAL DYSFUNCTION AND DISORDERS OF MALE REPRODUCTIVE HEALTH

4.1 Erectile dysfunction

Epidemiological data have shown a high prevalence and incidence of ED worldwide [185]. Among others, the Massachusetts Male Aging Study (MMAS) [186] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [187]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [188] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [189]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [190]. Differences among these studies can be explained by differences in methodology, ages, and socio-economic and cultural status of the populations studied. The prevalence rates of ED studies are reported in Table 7.

4.2 Premature ejaculation

As evidenced by the highly discrepant prevalence rates reported in Table 8 [191], the method of recruitment for study participation, method of data collection and operational criteria can all greatly affect reported prevalence rates of premature ejaculation (PE). The major problem in assessing the prevalence of PE was the lack of a universally recognised definition at the time the surveys were conducted [192]. Vague definitions without specific operational criteria, different manners of sampling, and non-standardised data acquisition have led to heterogeneity in estimated prevalence [192-196]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLS), which determines adult sexual behaviour in the USA [197]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20-30% based on the relatively low number of men who seek medical help for PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower [198]. Two separate observational, cross-sectional surveys from different continents found that overall prevalence of PE was 19.8 and 25.8%, respectively [199, 200]. Further stratifying these complaints into the classifications defined by Waldinger *et al.* [201], rates of lifelong PE were 2.3 and 3.18%, acquired PE 3.9 and 4.48%, variable PE 8.5 and 11.38% and subjective PE 5.1 and 6.4% [199, 200]. Both studies showed that men with acquired PE were more likely to seek treatment compared to men with lifelong PE. Treatment-seeking behaviour may have contributed to errors in the previously reported rates of PE, as it is possible that men with lifelong PE came to terms with their problem and did not seek treatment. The additional psychological burden of a new change in ejaculatory latency in acquired PE may have prompted more frequent treatment seeking [202]. Thus, it is likely that there is disparity between the incidence of the various PE sub-types in the general community and in men actively seeking treatment for PE [203, 204]. This disparity could be a further barrier to understanding the true incidence of each sub-type of PE. An approximately 5% prevalence of acquired PE and lifelong PE in the general population is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency of < 2 minutes [205].

4.3 Other ejaculatory disorders

*4.3.1 **Delayed ejaculation***

Due to its rarity and uncertain definitions, the epidemiology of delayed ejaculation (DE) is not clear [206]. However, several well-designed epidemiological studies have revealed that its prevalence is around 3% among sexually active men [197, 207]. According to data from the NHSLS, 7.78% of a national probability sample of 1,246 men aged 18-59 years reported inability achieving climax or ejaculation [197]. In a similar stratified national probability sample survey completed over 6 months among 11,161 men and women aged 16-44 years in Britain, 0.7% of men reported inability to reach orgasm [208]. In an international survey of sexual problems among 13,618 men aged 40–80 years from 29 countries, 1.1-2.8% of men reported that they frequently experience inability to reach orgasm [209]. Another study conducted in the United States (USA), in a national probability sample of 1,455 men aged 57-85 years, 20% of men reported inability to climax and 73% reported that they were bothered by this problem. [210]. Considering the findings of these epidemiological studies and their clinical experiences, some urologists and sex therapists have postulated that the prevalence of DE may be higher among older men [211-213]. Similar to the general population, the prevalence of men with DE is low among patients who seek treatment for their sexual problems. An Indian study that evaluated the data on 1,000 consecutive patients with sexual disorders who attended a psychosexual clinic demonstrated that the prevalence of DE was 0.6% and it was more frequent in elderly people with diabetes [214]. Nazareth *et al.* [215] evaluated the prevalence of International Classification of Diseases 10th edition (ICD-10) diagnosed sexual dysfunctions among 447 men attending 13 general practices in London, UK and found that 2.5% of the men reported inhibited orgasm during intercourse. Similar to PE, there are distinctions among lifelong, acquired and situational DE [216]. Although the evidence is limited, the prevalence of lifelong and acquired DE is estimated at 1 and 4%, respectively [217].

*4.3.2 **Anejaculation and Anorgasmia***

Establishing the exact prevalence of anejaculation and anorgasmia is difficult since many men cannot distinguish between ejaculation and orgasm. The rarity of these clinical conditions further hampers the attempts to conduct epidemiological studies. In a report from the USA, 8% of men reported unsuccessfully achieving orgasm during the past year [197].

According to Kinsey *et al.* [218], 0.14% of the general population have anejaculation. The most common causes of anejaculation were spinal cord injury, diabetes mellitus and multiple sclerosis. Especially in most cases of spinal cord injury, medical assistance is the only way to ejaculate. While masturbation leads to the lowest rates of ejaculation, higher response rates can be obtained with penile vibratory stimulation or acetylcholine esterase inhibitors followed by masturbation in patients with spinal cord injury [219].

4.3.3 *Retrograde ejaculation*

Similar to anejaculation, it is difficult to estimate the true incidence of retrograde ejaculation (RE). Although RE is generally reported in 0.3-2% of patients attending fertility clinics [220], diabetes may increase these rates by leading to autonomic neuropathy. Autonomic neuropathy results in ED and ejaculatory dysfunctions ranging from DE to RE and anejaculation, depending on the degree of sympathetic autonomic neuropathy involved [221]. In 54 diabetic patients with sexual dysfunction, RE was observed with a 6% incidence [222]. In a controlled trial, RE was observed in 34.6% of diabetic men [223]. A more recent trial reported the rate of RE among 57 type-1-diabetes mellitus patients (aged 18-50 years) was at least 8.8% [224]. Retrograde ejaculation was also reported in studies of patients who had undergone transurethral resection of prostate (TURP) or open prostatectomy due to disrupted bladder neck integrity. A study of the effect of prostatectomy on QoL in 5,276 men after TURP, found that 68% reported post-surgical RE [225]. However, with the development of less invasive techniques, the incidence of RE decreases following the surgical treatment of LUTS [226-230].

4.3.4 *Painful ejaculation*

Painful ejaculation is a common but poorly understood clinical phenomenon, which is associated with sexual dysfunction. Several studies demonstrated its prevalence to range between 1-10% in the general population [231-233]; however, it may increase to 30-75% among men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [234-238]. It should be noted that the design of most of these studies was not scientifically sound and the condition was probably under-reported due to the lack of an evidence-based definition and well-defined prognostic criteria.

4.3.5 *Haemospermia*

The exact incidence and prevalence of haemospermia are difficult to elucidate due to a number of factors including its covert presentation, usually self-limiting nature and patient embarrassment. The symptom represents 1-1.5% of all urological referrals and occurs in all age groups, with a mean age of 37 years [239, 240]. In a PCa screening study of 26,126 men, aged ≥ 50 years or older than 40 with a history of PCa or of black ethnicity, haemospermia was found in 0.5% on entry to the trial [241].

4.4 Low sexual desire

The global prevalence of low sexual desire in men is 3-28% [209, 242, 243]. Low solitary and dyadic sexual desires, have been reported in 68% and 14% of men, respectively [244]. Also, low sexual desire has been observed as a common complaint in gay men, with a prevalence of 19-57% [245, 246]. Despite its relationship with age, low sexual desire has been reported among young men (18-29 years), with prevalence of 6-19% [197, 247, 248].

Table 7: Prevalence rates of erectile dysfunction [185]

Date	Authors	Population	Response rate	Age (years)	Measurement technique	Principal findings	Correlates
1993	Solstad *et al.* [249]	439 men; random population sample (Denmark)	81%	51	Interview and self-administered questionnaire	Overall, 4% of men had ED as assessed by questionnaire, interviews identified a higher frequency of ED (40%)	Not reported
1994	Feldman *et al.* [186] **MMAS*	1,290 men; random population sample (United States)	40%	40-70	Self-administered questionnaire	Overall, 52% of men had ED 17.2% of men had minimal ED 25.2% of men had moderate ED 9.6% of men had complete ED	Age

1995	Panser *et al.* [250]	2,155 men; random population sample (United States)	55%	40-79	Self-administered questionnaire	1% ED in men aged 40-49 years 6% ED in men aged 50-59 years 22% ED in men aged 60-69 years 44% ED in men aged 70-79 years	
1996	Helgason *et al.* [251]	319 men; random population sample (Sweden)	73%	50-80	Self-administered questionnaire	3% ED in men aged 50–59 years 24% ED in men aged 60–69 years 49% ED in men aged 70–80 years	Age, Prostate cancer, Diabetes, Myocardial infarction, Diuretic use, Warfarin use, H2 receptor blocker use
1996	MacFarlane *et al.* [252]	1,734 men; random population sample (France)	86%	50-80	Self-administered questionnaire	20% ED in men aged 50–59 years 33% ED in men aged 60–69 years 38% ED in men aged 70–80 years	Age
1996	Fugl-Meyer [242]	1,288 men; random population sample men (Sweden)	52%	18-74	Structured interview	Overall, 5% of men had ED 3% ED in men aged 18–24 years 2% ED in men aged 25–34 years 2% ED in men aged 35–49 years 7% ED in men aged 50–65 years 24% ED in men aged 66–74 years	Age
1999	Laumann *et al.* [197] **NHSLS*	1,244 men; random population sample (United States)	70%	18-59	Structured interview	Overall, 10% of men had ED (moderate plus severe) 7% ED in men aged 18–29 years 9% ED in men aged 30–39 years 11% ED in men aged 40–49 years 18% ED in men aged 50–59 years	Age, Race, Emotional stress, Urinary symptoms, Poor health, Low income
1999	Pinnock *et al.* [253]	427 men; random population sample (Australia)	69.8%	> 40	Self-administered questionnaire	6% ED in men aged 40–49 years 12% ED in men aged 50–59 years 41% ED in men aged 60–69 years 63% ED in men aged 70–79 years 81% ED in men aged 80+ years	Age, Hyper-cholesterolemia,
2000	Braun *et al.* [187] (COLOGNE Study)	8,000 men	56%	30-80	Self-administered questionnaire by mail (Cologne ED Questionnaire)	Prevalence of ED was 19.2%	Age, Hypertension, Diabetes, Pelvic surgery, LUTS

2001	Moreira *et al.* [254]	1,170 men; attending public places (heavy bias toward younger men) (Brazil)	91%	>18	Self-administered questionnaire	Overall, 14.7% of men had ED (moderate plus severe); 9.4% ED in men aged 18–39 years 15.5% ED in men aged 40–49 years 22.1% ED in men aged 50–59 years 37% ED in men aged 60–69 years 39.6% ED in men aged >70 years	Age, Education, Racial origin, Diabetes, Hypertension, Depression
2001	Meuleman *et al.* [255]	1,233 men; random population sample (the Netherlands)	70%	40-79	Self-administered questionnaire	Overall, 13% of men had ED 6% ED in men aged 40–49 years 9% ED in men aged 50–59 years 22% ED in men aged 60–69 years 38% ED in men aged 70–79 years	Age
2001	Blanker *et al.* [232, 256]	1,688 men; random population sample (the Netherlands)	50%	50-75	Self-administered questionnaire	3% ED in men aged 50–54 years 5% ED in men aged 55–59 years 11% ED in men aged 60–64 years 19% ED in men aged 65–69 years 26% ED in men aged 70–78 years	Age, Smoking, Obesity, LUTS, COPD, Treatment for CV disease
2001	Martin-Morales *et al.* [257]	2,476 men; random population sample (Spain)	75%	25-70	Self-administered questionnaire and single question	Overall, 12.1% of men had ED (single question) and 18.9% for questionnaire According to single question: 3.9% ED in men aged 25–39 years 6.3% ED in men aged 40–49 years 15.9% ED in men aged 50–59 years 32.2% ED in men aged 60–70 years IIEF identified milder ED, and single question identified more moderate and severe ED	Age, Hypertension, Diabetes, Cardiac disease, Pulmonary disease, Circulatory disease, Rheumatic disease, High cholesterol, Prostatic disease, Allergy, Medication “for nerves”, Sleeping tablets, Heavy smoking, Alcohol abuse

2002	Moreira *et al.* [258]	602 men; random population sample (Brazil)	92%	40-70	Interview	Overall, 14.4% of men had ED (moderate or severe) 9.9% ED in men aged 40–49 years 11.8% ED in men aged 50–59 years 31.7% ED in men aged 60–69 years	Age, Marital status, Diabetes, Depression, IPSS, Decreased physical activity
2002	Moreira *et al.* [258]	342 men; random population sample (Brazil)	47.6%	40-70	Self-administered questionnaire	Overall, 12.0% of men had ED (moderate or severe) 3.5% ED in men aged 40–49 years 16.7% ED in men aged 50–59 years 39.6% ED in men aged 60–69 years	Age, Diabetes, Hypertension, Heavy smoking
2002	Morillo *et al.* [259]	1,963 men; random population sample (Columbia, Venezuela and Ecuador)	82%	> 40	Standardised questionnaire	Overall, 19.8% of men had ED (moderate or severe)	Age, Diabetes, Hypertension, BPH
2003	Richters *et al.* [260]	8,517 men; random population sample (Australia)	69.4%	16-59	Computer-assisted telephone interview	Overall, 9.5% of men had ED 4.3% ED in men aged 16–19 years 4.5% ED in men aged 20–29 years 5.1% ED in men aged 30–39 years 12.5% ED in men aged 40–49 years 19.2% ED in men aged 50–59 years	Age
2003	Rosen *et al.* [261]	12,815 men; random population sample (multinational: United States, United Kingdom, France, Germany, the Netherlands, Italy, Spain)	36.8%	50-80	Self-administered questionnaire (IIEF and DAN-PSS)	According to DAN-PSS: Overall, 48.9% of men had ED 30.8% ED in men aged 50-59 years 55.1% ED in men aged 60-69 years 76% ED in men aged 70-80 years	Age, LUTS, Diabetes, Hypertension, Cardiac disease, Hyperlipidemia, Tobacco use

2004	Rosen *et al.* [262] **MALES*	27,839 men random population sample (multinational: United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil)	US: 45%; UK: 48%; Germany: 45%; France: 48%; Italy: 53%; Spain: 50%; Mexico: 55% and Brazil: 51%.	20-75	Random digit dialing and interviewed via computer-assisted telephone interviewing. A standardised questionnaire	Overall prevalence of ED in the MALES sample was 16%	Age, Hypertension, Heart trouble or angina, High cholesterol, Diabetes, Depression or anxiety
2004	Shiri *et al.* [263]	2,198 men; stratified birth cohort (Finland)	70%	50,60, and 70 at first survey 55, 65, and 75 at second survey	Self-administered questionnaire at two separate time points, 5 years apart	48% of men had minimal ED 15.2% of men had moderate ED 13.2% of men had complete ED	Age, Diabetes, Hypertension, Heart disease, Cerebrovascular disease,Smoking
2005	Laumann *et al.* [209] **GSSAB*	13,750 men; random population sample (world)	19%	40-80	Telephone survey (random dialed digit)	Overall: In Northern Europe, 13.3% had ED In Southern Europe, 12.9% had ED In non-European West, 20.6% had ED In Central/South America, 13.7% had ED In Middle East, 14.1% had ED In East Asia, 13.3% had ED In Southeast Asia, 28.1% had ED	Age
2005	Moreira *et al.* [264]	750 men; random population sample (Spain)	23%	40-80	Telephone survey (random digit dialing)	Overall, 12.7% had ED	Age
2005	Moreira *et al.* [265]	750 men; random population sample (Germany)	17.4%	40-80	Telephone survey (random digit dialing)	Overall, 7.9% had ED	Age
2005	Moreira Junior *et al.* [265]	471 men; random population sample (Brazil)	18%	40-80	Telephone survey (random digit dialing)	Overall, 13.1% of men had ED	Age, Depression
2006	Brock *et al.* [266]	500 men; random population sample (Canada)	9.7%	40-80	Telephone survey (random digit dialing)	Overall, 16% of men had ED	Age, Depression, Diabetes

2007	De Almeida Claro *et al.* [267]	2,000 men; random population study (Brazil)	Not reported	>20	Standardised interview with self-reported questionnaire (IIEF)	Overall, 1.7% of men had ED 0.2% ED in men aged 20-30 years 0.22% ED in men aged 31-40 years 1.0% ED in men aged 41-50 years 2.8% ED in men aged 51-60 years 7.0% ED in men aged > 61 years	Age
2007	Ahn *et al.* [268]	1,570 men; geographically stratified random population study	Not reported	40-79	Self-administered questionnaire (IIEF-5)	Overall, 13.4% had self-reported ED ED prevalence as defined by IIEF-5 score less than 17 was 32.4% According to single question: 4.2% ED in men aged 40-49 years 13.0% ED in men aged 50-59 years 30.1% ED in men aged 60-69 years 41.1% ED in men aged 70-79 years	Age, Single status, Low income, Diabetes, Hypertension, Hyperlipidemia, Heart disease, Musculoskeletal disorders, Alcohol, Depression, Coffee intake
2008	Moreira *et al.* [269]	750 men; random population sample (Australia)	16.9%	40-80	Telephone survey (random digit dialing)	Overall, 32% of men had ED	Age
2008	Chew *et al.* [270]	1,580 men; random population sample (Australia)	37.3%	>20	Postal survey Self-administered questionnaire (IIEF-5)	15.7% ED in men aged 20-29 years 8.7% ED in men aged 30-39 years 12.9% ED in men aged 40-49 years 31.6% ED in men aged 50-59 years 52.4% ED in men aged 60-69 years 69.4% ED in men aged 70-79 years 68.2% ED in men aged > 80 years	Age, Marital status
2008	Teles *et al.* [271]	3,067 men; random population sample (Portugal)	81.3%	40-69	Self-administered questionnaire, including IIEF	Overall, 48.1% of men had ED 29% ED in men aged 40-49 years 50% ED in men aged 50-59 years 74% ED in men aged 60-69 years	Age, Diabetes, Cardiac insufficiency, Psychiatric illness
2008	Moreira *et al.* [272]	750 men; random population sample (United Kingdom)	17%	40-80	Telephone survey (random digit dialing)	Overall, 17.8% of men had ED	Age

2009	Laumann *et al.* [273]	742 men; random population sample (United States)	9%	40-80	Telephone survey (random digit dialing)	Overall, 22.5% of men had ED	Age, Depression
2009	Buvat *et al.* [274]	750 men; random population sample (France)	23.8%	40-80	Telephone survey (random digit dialing)	Overall, 15% of men had ED	Age
2010	Corona *et al.* [275]	3,369 men; random population study (Europe: Italy, Belgium, United Kingdom, Spain, Poland, Hungary, Estonia)	40%	40-80	Self-administered questionnaire	Overall, 30% of men had ED 6% ED in men aged 40-49 years 19% ED in men aged 50-59 years 38% ED in men aged 60-69 years 64% ED in men 70 and over	Age, Depression, LUTS, Cardiovascular disease, Diabetes, Obesity
2016	Oyelade *et al.* [276]	241 men; random sampling cross-sectional population based survey (Nigeria)	99%	30-80	Self-administered questionnaire (IIEF-5)	General prevalence of ED was 58.9%	Age, Hypertension, Use of anti-hypertensive drugs, Diabetes mellitus, Heart disease
2017	Cayan *et al.* [277]	2,760 men; random population study (Turkey)	Non-reported	≥ 40	Self-administered questionnaire (IIEF-5)	Prevalence of ED was calculated as 33% among all men aged ≥ 40 years. ED prevalence rates were 17% for 40-49 years, 35.5% for 50-59 years, 68.8% for 60-69 years, and 82.9% for ≥ 70 years	Age, Diabetes, Hypertension, Atherosclerosis, Dyslipidaemia, LUTS, Educational status, Monthly income
2017	Quilter *et al.* [278]	Randomly selected age-stratified population-based sample of 2,000 men (New Zealand)	30%	40-70	Self-reported erectile function (IIEF-5) and a single-question self-assessment tool.	Prevalence of ED was 42% (22% mild, 10% mild to moderate, 6% moderate, and 4% severe)	Age, Anxiety or depression

2021	Calzo *et al.* [279]	2,660 sexually active men (USA)	Not reported	18-31	Self-administered questionnaire (IIEF-5)	Prevalence of mild ED was 11.3% and moderate-to-severe ED was 2.9%	Demographic (age; marital status) Metabolic (body mass index; waist circumference; history of diabetes, hypertension, hyperch olesterolaemia) Mental health (depression, anxiety, antidepressant, tranquiliser use)
2020	Goldstein *et al.* [280]	97,159 men from the 2015 and 2016 National Health and Wellness Surveys (Italy, France, China, Spain, Germany, US, UK, Brazil)	Not reported	≥ 18	Self-reported experiencing difficulty in achieving or maintaining an erection in the past 6 months (Erection difficulty was rated on a scale from 1= not at all to 5 = a great deal; those who selected a response of ≥ 2 were categorised as having ED and included in the study)	Prevalence of ED by country among adult males ≥ 18: Italy = 48.6% France = 44.9% Germany = 44.9% Spain = 43.5% UK = 42.6% US = 42% China = 41.6% Brazil = 37.2% 40-70: Italy = 52.2% France = 47.8% China = 47.4% Spain = 46.6% Germany = 46.1% US = 46.1% UK = 42.6% Brazil = 42.1%	Age/BPH
2020	Molina-Vega *et al.* [281]	254 young non-diabetic obese men	Not reported	18-49	Self-administered questionnaire (IIEF-5)	Prevalence of ED was 42.1%	Age, components of metabolic syndrome

Four baseline studies estimating the prevalence of Erectile Dysfunction:
MMAS = the Massachusetts Male Aging Study; NHSLS = the National Health of Social Life Survey; MALES = the multi-national men's attitudes to life events and sexuality; GSSAB = Global Study of Sexual Attitudes and Behaviours.
BPH = Benign Prostate Hyperplasia; COPD = Chronic Obstructive Pulmonary Disease; ED = Erectile Dysfunction; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = Lower urinary tract symptoms.

Table 8: The prevalence rates of premature ejaculation [191]

Date	Authors	Method of Data Collection	Method of Recruitment	Operational Criteria	Prevalence Rate	Number of Men
1998	Dunn *et al.* [282]	Mail	General practice registers - random stratification	Having difficulty with ejaculating prematurely	14% (past 3 mo)	617
					31% (lifetime)	618
1999	Laumann *et al.* (NHSLS) [197]	Interview	NA	Climaxing/ ejaculating too rapidly during the past 12 months	31%	1,410

2002	Fugl-Meyer and Fugl-Meyer [283]	Interview	Population register	NA	9%	1,475
2004	Rowland *et al.* [284]	Mailed questionnaire	Internet panel	DSM IV	16.3%	1,158
2004	Nolazco *et al.* [285]	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	28.3%	2,456
2005	Laumann *et al.* [209]	Telephone-personal interview/mailed questionnaires	Random (systematic) sampling	Reaching climax too quickly during the past 12 months	23.75% (4.26% frequently)	13,618
2005	Basile Fasolo *et al.* [286]	Clinician-based	Invitation to outpatient clinic	DSM IV	21.2%	12,558
2005	Stulhofer *et al.* [287]	Interview	Stratified sampling	Often ejaculating in less than < 2 minutes	9.5%	601
2007	Porst *et al.* (PEPA) [198]	Web-based survey Self-report	Internet panel	Control over ejaculation, distress	22.7%	12,133
2008	Shindel *et al.* [288]	Questionnaire	Male partners of infertile couples under evaluation	Self-report premature ejaculation	50%	73
2009	Brock *et al.* [289]	telephone interview	Web-based survey	DSM III	16%	3,816
				Control	26%	
				Distress	27%	
2010	Traeen and Stigum [248]	Mailed questionnaire + internet	Web interview + Randomisation		27%	11,746 + 1,671
2010	Son *et al.* [290]	Questionnaire	Internet panel (age < 60 years)	DSM IV	18.3%	600
2010	Amidu *et al.* [291]	Questionnaire	NA	NA	64.7%	255
2010	Liang *et al.* [292]	NA	NA	ISSM	15.3%	1,127
2010	Park *et al.* [293]	Mailed questionnaire	Stratified sampling	Suffering from PE	27.5%	2,037
2010	Vakalopoulos *et al.* [294]	One-on-one survey	Population-based cohort	EED	58.43%	522
				ISSM lifelong PE	17.7%	
2010	Hirshfeld *et al.* [245]	Web-based survey	Online advertisement in the United States and Canada	Climaxing/ ejaculating too rapidly during the past 12 months	34%	7,001
2011	Christensen *et al.* [295]	Interview + questionnaire	Population register (random)	NA	7%	5,552
2011	Serefoglu *et al.* [199]	Interview	Stratified sampling	Complaining about ejaculating prematurely	20.0%	2,593
2011	Son *et al.* [296]	Questionnaire	Internet panel	Estimated IELT ≤ 5 mins, inability to control ejaculation, distress	10.5%	334
2011	Tang and Khoo [297]	Interview	Primary care setting	PEDT ≥ 9	40.6%	207
2012	Mialon *et al.* [298]	Mailed questionnaire	Convenience sampling (age 18-25 years)	Control over ejaculation Distress	11.4%	2,507
2012	Shaeer and Shaeer [299]	Web-based survey	Online advertisement in Arabic countries	Ejaculate before the person wishes to ejaculate at least sometimes	83.7%	804

2012	Shindel *et al.* [300]	Web-based survey	Online advertisement targeted to MSM + distribution of invitation to organisations catering to MSM	PEDT ≥ 9	8-12%	1,769
2012	McMahon *et al.* [301]	Computer assisted interviewing, online, or in-person self-completed	NA	PEDT ≥ 11	16%	4,997
				Self-Reported (always/nearly-always)	13%	
2012	Lotti *et al.* [302]	Interview	Men seeking medical care for infertility	PEDT ≥ 9	15.6%	244
2013	Zhang *et al.* [303]	Interview	Random stratified sample of married men aged 30-60	Self-reported premature ejaculation	4.7%	728
2013	Lee *et al.* [304]	Interview	Stratified random sampling	PEDT ≥ 11	11.3%	2,081
				Self-Reported	19.5%	
				IELT<1 min	3%	1,035
2013	Gao *et al.* [200]	Interview	Random stratified sample of monogamous heterosexual men in China	Self-reported premature ejaculation	25.8%	3,016
2013	Hwang *et al.* [305]	Survey of married couples	Married heterosexual couples in Korea	Estimated IELT < 2 minutes	21.7%	290
				PEDT > 11	12.1%	
2013	Vansintejan *et al.* [306]	Web Based survey	Online and flyer advertisements to Belgian men who have sex with men (Only HIV+ men in this study)	IPE score ≤ 50% of total possible	4%	72
2013	Shaeer *et al.* [307]	Web Based survey	Targeting English-speaking men aged > 18 years, living most of their lives in the USA, regardless of personal interests and web browsing preferences	ISSM definition [179]	6.3%	1133
				PEDT	49.6%	
				Unfiltered self-reported	77.6%	
				Filtered self-reported	14.4%	
2016	Karabakan [308]	Interview (heavy bias toward younger men)	Targeting police academy students aged 24-30 years who applied for routine urological examination	PEDT > 10	9.2%	1000
2017	Gao *et al.* [309]	Field survey with face-to-face interviews	Comprising men aged 20-68 years in five cities in the Anhui province	Self-estimated IELT	Lifelong PE 10.98%	1239

DMS = Diagnostic and Statistical Manual of Mental Disorders; NA = not applicable; ISSM = International Society for Sexual Medicine; PEDT = Premature Ejaculation Diagnostic Tool; IELT = intravaginal ejaculatory latency time; IPE = Index of Premature Ejaculation; mo = months.

5. MANAGEMENT OF ERECTILE DYSFUNCTION

5.1 Definition and classification

Penile erection is a complex physiological process that involves integration of both neural and vascular events, along with an adequate endocrine milieu. It involves arterial dilation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [310]. Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [311]. Erectile dysfunction may affect psychosocial health and have a significant impact on the QoL of patients and their partner's [186, 312-314].

There is established evidence that the presence of ED increases the risk of future CV events including myocardial infarction, cerebrovascular events, and all-cause mortality, with a trend towards an increased risk of cardiovascular mortality [315]. Therefore, ED can be an early manifestation of coronary artery and peripheral vascular disease and should not be regarded only as a QoL issue, but also as a potential warning sign of CVD [316-319]. A cost analysis showed that screening men presenting with ED for CVD represents a cost-effective intervention for secondary prevention of both CVD and ED, resulting in substantial cost savings relative to identification of CVD at the time of presentation [320].

Erectile dysfunction is commonly classified into three groups based on aetiology: organic, psychogenic and mixed ED. However, this classification should be used, with caution as most cases are actually of mixed aetiology. It has therefore been suggested to use the terms "primary organic" or "primary psychogenic".

5.2 Risk factors

Erectile dysfunction is associated with unmodifiable and modifiable common risk factors including age, diabetes mellitus, dyslipidaemia, hypertension, CVD, BMI/obesity/waist circumference, MetS, hyperhomocysteinemia, lack of exercise, and smoking (a positive dose-response association between quantity and duration of smoking has been demonstrated) [313, 317, 321-329]. Furthermore, an association between ED status and pharmaco-therapeutic agents for CVD (e.g., thiazide diuretics and β-blockers, except nebivolol), exert detrimental effects on erectile function, whereas newer drugs (i.e., angiotensin-converting enzyme-inhibitors, angiotensin-receptor-blockers and calcium-channel-blockers) have neutral or even beneficial effects [317, 330, 331]. Furthermore, the use of psychotropic drugs increases the risk of developing ED [332]. Atrial fibrillation [333], hyperthyroidism [20], vitamin D deficiency [334, 335], hyperuricemia [336], folic acid deficiency [337], depression [338] and anxiety disorders [339], chronic kidney disease [328], rheumatic disease [340], stroke [341] and chronic obstructive pulmonary disease [342] have also been reported as risks factors. Available data do not confirm a clear association between ED and hypothyroidism and hyperprolactinaemia [20]. Interestingly, a dual (cause-effect) association between ED and osteoporosis had been proposed, and therefore ED patients should be evaluated by bone mineral density or men with osteoporosis should be further assessed for erectile function [343]. Current evidence supports the fact that renal transplantation improves erectile function and the risk of ED is progressively reduced from before to after surgery [344, 345].

Further epidemiological data have also highlighted other potential risk factors associated with ED including sleep disorders [346], obstructive sleep apnoea [347], psoriasis [348-350], gouty arthritis [346] and ankylosing spondylitis [351], non-alcoholic fatty liver disease [352], other chronic liver disorders [353], chronic periodontitis [354], open-angle glaucoma [355], inflammatory bowel disease [356], chronic fatigue syndrome [357] and allergic rhinitis [358], and spina bifida [359]. Insufficient data are currently available to correlate primarily organic or primarily psychogenic ED with SARS-CoV-2 infection associated disease (COVID-19) [360, 361]. Similarly, although currently available data are scarce, a positive correlation between cycling and ED had been proposed, even if only after adjusting for age and several comorbidities [362]. Recent findings show that pelvic ring fractures are associated with onset of ED with important influence on QoL, especially in young patients [363, 364].

A recent meta-analysis showed that men partnered with women suffering from Female Sexual Dysfunction (FSD) present an increased risk of developing sexual impairment, in particular erectile and ejaculatory dysfunction [365].

Erectile dysfunction is also frequently associated with other urological conditions and procedures (Table 9). Epidemiological studies have demonstrated consistent evidence for an association between LUTS/BPH and sexual dysfunction, regardless of age, other co-morbidity and lifestyle factors [366]. The Multinational Survey on the Aging Male study, performed in the USA, France, Germany, Italy, Netherlands, Spain, and the UK, systematically investigated the relationship between LUTS and sexual dysfunction in > 12,000 men aged 50-80 years. In the 83% of men who were reported to be sexually active, the overall prevalence of LUTS was 90%, with an overall 49% prevalence of ED and a reported complete absence of erections in 10% of patients. The

overall prevalence of ejaculatory disorders was 46% [261]. Regardless of the employed technique, surgery for BPH-LUTS had no significant impact on erectile function at long-term (5 year) follow-up, while a slight advantage is demonstrated for prostate urethral lift (PUL) over conventional TURP at 24 months follow-up [367]. A post-operative improvement of erectile function was even found depending on the degree of LUTS improvement [368, 369]. An association has been confirmed between ED and CP/CPPS [369], and bladder pain syndrome/interstitial cystitis (BPS/IC), mostly in younger men [370]. An association between ED and PE has also been demonstrated (see Section 6.2) [371]. Recent evidence showed that ED is a mild, short-term and transient complication of prostate biopsy, regardless of the trans-rectal or trans-perineal approach employed [372].

An increased risk of ED is reported following [373] open urethroplasty, especially for correction of posterior strictures [374], with recent findings emphasising the importance of patient-reported outcome measures (PROMs) in urethral reconstructive surgery to better report actual sexual function outcomes [375, 376].

Table 9: Urological conditions associated with ED

Urological Condition	Association with ED
LUTS/BPH [366]	Depending on the severity of LUTS and patients' age/population characteristics: Odds ratio (OR) of ED among men with LUTS/BPH ranges from 1.52 to 28.7 and prevalence ranges from 58% to 80%
Surgery for BPH/LUTS (TURP, laser, open, laparoscopic, etc.) [368]	Overall, absence of significant variations in terms of erectile function scores after surgery
Chronic Prostatitis/Chronic Pelvic Pain Syndrome [369]	Prevalence of ED among patients with CP/CPPS 29% [24%-33%, 95%CI], Range: 11% - 56% among studies
Bladder Pain Syndrome/Interstitial Cystitis [370]	OR of BPS/IC among patients with ED. Overall: OR (adjusted) = 1.75 [1.12 – 2.71, 95% CI] Age ≥ 60: OR (adjusted) = 1.07 [0.41 – 2.81, 95% CI] Age 40-59: OR (adjusted) = 1.44 [1.02 – 2.12, 95% CI] Age 18-39: OR (adjusted) = 10.40 [2.93 – 36.94, 95% CI]
Premature Ejaculation [373]	OR of ED among patients with PE = 3.68 [2.61 – 5.68, 95% CI]
Urethroplasty surgery for posterior urethral strictures [374]	OR of ED after posterior urethroplasty = 2.51 [1.82 – 3.45, 95% CI]

CI = confidence interval; OR = odds ratio; TURP = transurethral resection of the prostate; ED = erectile dysfunction; BPS/IC = bladder pain syndrome/interstitial cystitis; LUTS = lower urinary tract symptoms.

Several studies have shown that lifestyle modification [377], including physical activity [378], weight loss [379] and pharmacotherapy [331, 380, 381] for CVD risk factors may be of help in improving sexual function in men with ED. Meta-analytic data reveals a positive effect of lipid-lowering therapy with statins on erectile function [382, 383]. However, it should be emphasised that further controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in the prevention and treatment of ED [377].

5.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 10) [310]. In most cases, numerous pathophysiological pathways can co-exist and may all negatively impact on erectile function.

The proposed ED etiological and pathophysiological division should not be considered prescriptive. In most cases, ED is associated with more than one pathophysiological factor and very often, if not always, will have a psychological component. Likewise, organic components can negatively affect erectile function with different pathophysiological effects. Therefore, Table 10 must be considered for diagnostic classifications only (along with associated risk factors for each subcategory).

Table 10: Pathophysiology of ED

Vasculogenic
Recreational habits (i.e., cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g., hypertension, coronary artery disease, peripheral vasculopathy)
Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia
Major pelvic surgery (e.g., radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)
Neurogenic
Central causes
Degenerative disorders (e.g., multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
Peripheral causes
Type 1 and 2 diabetes mellitus
Chronic renal failure, chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, open urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumours of the external genitalia)
Hormonal
Diabetes mellitus; Metabolic Syndrome;
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiological pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, metabolic syndrome, chronic kidney disease, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, chronic obstructive pulmonary disease, rheumatic disease)
Psoriasis, gouty arthritis, ankylosing spondylitis, non-alcoholic fatty liver disease, chronic periodontitis, open-angle glaucoma, inflammatory bowel disease, chronic fatigue syndrome, allergic rhinitis, obstructive sleep apnoea, depression
Iatrogenic causes (e.g. TRUS-guided prostate biopsy)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, excessive alcohol intake)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5α-reductase inhibitors.

**A symmetry analysis showed that cardiovascular drugs do not strongly affect the risk of subsequently being prescribed as anti-erectogenic drug. The analysis only assessed the short-term risk [384].*

*5.3.1 **Pelvic surgery and prostate cancer treatment***

Pelvic surgery, especially for oncological disease (e.g., radical prostatectomy (RP) [385] or radical cystectomy [386] and colorectal surgery [387]), may have a negative impact on erectile function and overall sexual health. The most relevant causal factor is a lesion occurring in the neurovascular bundles that control the complex mechanism of the cavernous erectile response, whose preservation (either partial or complete) during surgery eventually configures the so-called nerve-sparing (NS) approach [388]. Therefore, surgery resulting in damage of the neurovascular bundles, results in ED, although NS approaches have been adopted over the last few decades. This approach is applicable to all types of surgery that are potentially harmful to erectile function, although to date, only the surgical treatment of PCa has enough scientific evidence supporting its potential pathophysiological association with ED [389, 390]. However, even non-surgical treatments of PCa (i.e., radiotherapy, or brachytherapy) can be associated with ED [391, 392]. The concept of active surveillance for the treatment of PCa was developed to avoid over-treatment of non-significant localised low-risk diseases, while limiting potential functional adverse effects (including ED). However, it is interesting that data suggest that even active surveillance has a detrimental impact on erectile function (and sexual well-being as a whole) [393-395].

To date, some of the most robust data on PROMs including erectile function, comparing treatments for clinically localised PCa come from the Prostate Testing for Cancer and Treatment (ProtecT) trial, in which 1,643 patients were randomised to active treatment (either RP or RT) and active monitoring and were followed-up for 6 years [396]. Sexual function, including erectile function, and the effect of sexual function on QoL were assessed with the Expanded Prostate Cancer Index Composite with 26 items (EPIC-26) instrument [397, 398]. At baseline, 67% of men reported erections firm enough for sexual intercourse but this fell to 52% in the active monitoring group, 22% in the RT group, and 12% in the RP group, at 6-months' assessment. The worst trend over time was recorded in the RP group (with 21% erections firm enough for intercourse after 3 years vs. 17% after 6 years). In the RT group, the percentage of men reporting erections firm enough for intercourse increased between 6 and 12 months, with a subsequent decrease to 27% at 6-years assessment. The percentage declined over time on a yearly basis in the active monitoring group, with 41% of men reporting erections firm enough for intercourse at 3 years and 30% at 6 year evaluations [396].

Radical prostatectomy (open, laparoscopic or robot-assisted) is a widely performed procedure with a curative intent for patients presenting with clinically localised intermediate- or high-risk PCa and a life expectancy of > 10 years based on health status and co-morbidity [399]. This procedure may lead to treatment-specific sequelae affecting health-related QoL. Men undergoing RP (any technique) should be adequately informed before the operation that there is a significant risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie's-like disease, and changes in penile length [390, 392]. These outcomes have become increasingly important with the more frequent diagnosis of PCa in both younger and older men [400, 401]. Research has shown that 25-75% of men experience post-RP ED [402], even though these findings had methodological flaws; in particular, the heterogeneity of reporting and assessment of ED among the studies [389, 403]. Conversely, the rate of unassisted post-operative erectile function recovery ranged between 20 and 25% in most studies. These rates have not substantially improved or changed over the past 17 years, despite growing attention to post-surgical rehabilitation protocols and refinement of surgical techniques [403-405].

Overall, patient age, baseline erectile function and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [390, 400, 402, 406]. Regardless of the surgical technique, surgeons' experience may clearly impact on post-operative EF outcome; in particular when surgeons have a caseload greater than 25 radical prostatectomy cases per year or total cumulative experience of >1,000 prostatectomy cases results in better erectile function outcomes after RP [407]. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [400]. The recovery time following surgery is of clinical importance in terms of post-operative recovery of erectile function. Available data confirm that post-operative erectile function recovery can occur up to 48 months after RP [408]. Likewise, it has been suggested that post-operative therapy (any type) should be commenced as soon as possible after the surgical procedure [400, 402], although evidence suggests that the number of patients reporting return of spontaneous erectile function has not increased.

In terms of the effects of surgical interventions (e.g., robot-assisted RP [RARP] vs. other types of surgery), data are still conflicting. An early systematic review showed a significant advantage in favour of RARP in comparison with open retropubic RP in terms of 12-month potency rates [409], without significant differences between laparoscopic RP and RARP. Some recent reports confirm that the probability of erectile function recovery is

about twice as high for RARP compared with open RP [410]. More recently, a prospective, controlled, non-randomised trial of patients undergoing RP in 14 Swedish centres comparing RARP versus open retropubic RP, showed a small improvement in erectile function after RARP [411]. Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at 12 weeks [412]. More controlled prospective well-designed studies, with longer follow-up, are necessary to determine if RARP is superior to open RP in terms of post-operative ED rates [413]. To overcome the problem of heterogeneity in the assessment of erectile function, for which there is variability in terms of the PROMs used (e.g., International Index of Erectile Function [IIEF], IIEF-5, Expanded Prostate Cancer Index Composite with 26 items [EPIC 26], Sexual Health Inventory for Men, etc.) to measure potency or erectile function, the criteria used to define restoration of erectile function should be re-evaluated utilising objective and validated thresholds (e.g., normalisation of scores or return to baseline erectile function) [389].

Erectile dysfunction is also a common problem after both external beam radiation therapy (EBRT) and brachytherapy for PCa. A systematic review and meta-analysis including men treated with EBRT (65%), brachytherapy (31%) or both (4%) showed that the post-treatment prevalence of ED was 34% at 1 year and 57% at 5.5 years [414, 415]. Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at 5 years [416].

Recently other modalities have emerged as potential therapeutic options in patients with clinically-localised PCa, including whole gland and focal (lesion-targeted) treatments, to ablate tumours selectively while limiting sexual toxicity by sparing the neurovascular bundles. These include high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy), focal padeliporfin-based vascular-targeted photodynamic therapy and focal radiation therapy (RT) by brachytherapy or CyberKnife®. All these approaches have a less-negative impact on erectile function with many studies reporting a complete recovery at one-year follow-up [417]. However, prospective randomised controlled studies are needed to compare the functional and oncological outcomes using different treatment modalities [418, 419].

*5.3.2 **Summary of evidence on the epidemiology/aetiology/pathophysiology of ED***

Summary of evidence	LE
Erectile dysfunction is common worldwide.	2b
Erectile dysfunction shares common risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in BMI) can improve erectile function.	1b
Erectile dysfunction is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
Erectile dysfunction is common after RP, irrespective of the surgical technique used.	2b
Erectile dysfunction is common after external radiotherapy and brachytherapy.	2b
Erectile dysfunction is less common after cryotherapy and high-intensity focused US.	2b

5.4 Diagnostic evaluation (basic work-up)

*5.4.1 **Medical and sexual history***

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partners [420]. It is important to establish a relaxed atmosphere during history-taking. This will make it easier to ask questions about erectile function and other aspects of the patient's sexual history; and to explain the diagnosis and therapeutic approach to the patient and their partner. Figure 3 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

The sexual history must include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [421, 422]. Validated psychometric questionnaires, such as the IIEF [103] or its short version (i.e., Sexual Health Inventory for Men; SHIM) [103], help to assess the different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, intercourse satisfaction, and overall satisfaction), as well as the potential impact of a specific treatment modality. Similarly, structured interviews allow the identification and quantification of the different underlying factors affecting erectile function [423].

Psychometric analyses also support the use of the Erectile Hardness Score (EHS) for the assessment of penile rigidity in practice and in clinical trials research [424]. In cases of depressive mood, clinicians may use the Beck Depressive Inventory [425], which is one of the most recognised self-reported

measures in the field, takes approximately 10 minutes to complete, and assigns the patient to a specific level of depression (varying from “normal mood” to “extreme depression”).

Patients should always be screened for symptoms of possible hypogonadism (testosterone deficiency), including decreased energy and libido, and fatigue; potential cognitive impairment may be also observed in association with hypogonadism (see Sections 3.5 and 3.6), as well as for LUTS. In this regard, although LUTS/BPH in themselves do not represent contraindications to treatment for LOH, screening for LUTS severity is clinically relevant [7].

*5.4.2 **Physical examination***

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [426, 427]. A physical examination may reveal unsuspected diagnoses, such as Peyronie’s disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggestive of hypogonadism (e.g., small testes or alterations in secondary sexual characteristics).

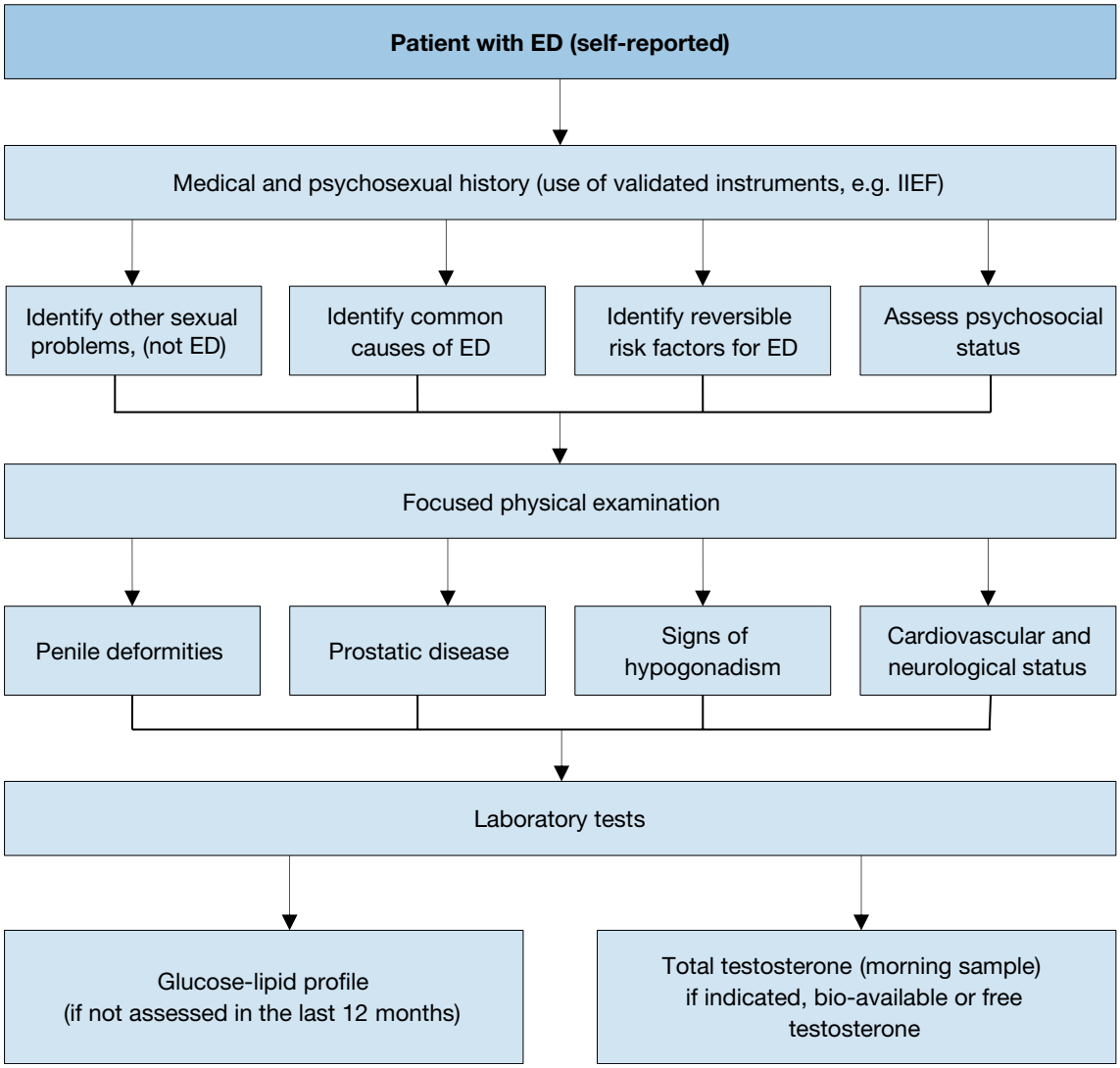
Assessment of previous or concomitant penile abnormalities (e.g., hypospadias, congenital curvature, or Peyronie’s disease with preserved rigidity) during the medical history and the physical examination is mandatory.

Blood pressure and heart rate should be measured if they have not been assessed in the previous 3-6 months. Likewise either BMI calculation or waist circumference measurement should be undertaken to assess patients for comorbid conditions (e.g., MetS).

*5.4.3 **Laboratory testing***

Laboratory testing must be tailored to the patient’s complaints and risk factors. Patients should undergo a fasting blood glucose or haemoglobin A1c and lipid profile measurement if they have not been assessed in the previous 12 months. Hormonal tests should include early morning total testosterone in a fasting state. The bio-available or calculated-free testosterone values may sometimes be needed to corroborate total testosterone measurements. However, the threshold of testosterone required to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism (see Sections 3.5 and 3.6) [20, 53, 428-430]. Additional laboratory tests may be considered in selected patients with specific signs and associated symptoms (e.g., PSA) [431], prolactin and luteinising hormone [432]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, clinical and biochemical evaluation presents an opportunity to identify comorbid conditions [427].

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with ED


Patient with ED (self-reported)
Medical and psychosexual history (use of validated instruments, e.g. IIEF)
Identify other sexual problems, (not ED)
Identify common causes of ED
Identify reversible risk factors for ED
Assess psychosocial status
Focused physical examination
Penile deformities
Prostatic disease
Signs of hypogonadism
Cardiovascular and neurological status
Laboratory tests
Glucose-lipid profile (if not assessed in the last 12 months)
Total testosterone (morning sample) if indicated, bio-available or free testosterone

ED = erectile dysfunction; IIEF = International Index of Erectile Function.

*5.4.4 **Cardiovascular system and sexual activity: the patient at risk***

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Epidemiological surveys have emphasised the association between cardiovascular/metabolic risk factors and sexual dysfunction in both men and women [433]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [434, 435]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease and stroke. Furthermore, the results of a recent prospective cohort study showed that ED is an independent predictor for incident atrial fibrillation [436]. All of these cause mortality and the increase is probably independent of conventional cardiovascular risk factors [316, 317, 437, 438]. Longitudinal data from an observational population-based study of 965 men without CVD showed that younger men (especially those < 50 years) with transient and persistent ED have an increased Framingham CVD risk [439].

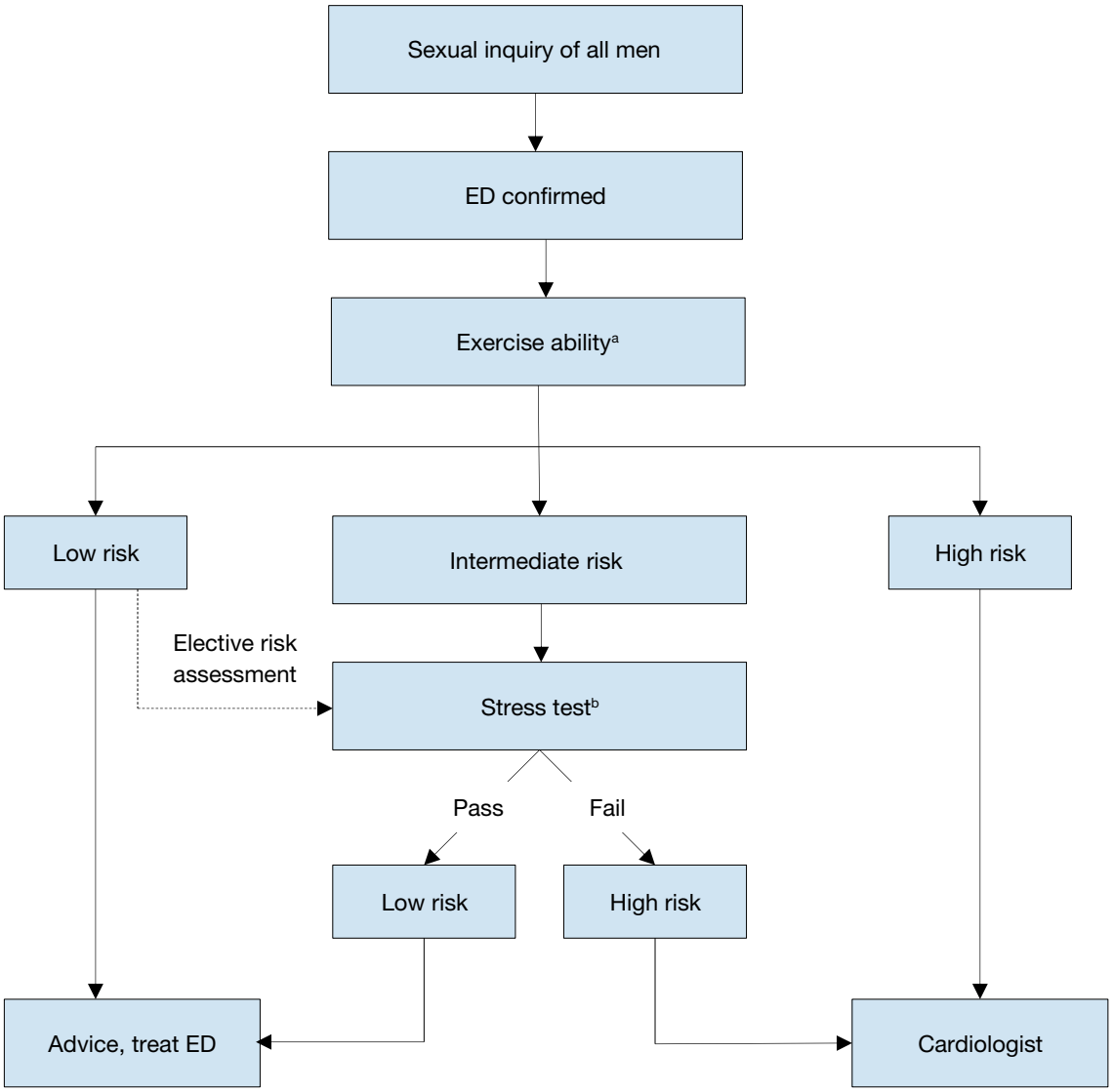
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [440]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [440-442]. Accordingly, patients with ED can be stratified into three cardiovascular risk categories (Table 11), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 3). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history [381].

Table 11: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus) [440, 442]

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Figure 4: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [440]



[a] *Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.*

[b] *Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.*

5.4.4.1 *Low-risk category*

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low-risk is typically implied by the ability to perform exercise of modest intensity, which is defined as, ≥ 6 metabolic equivalents of energy expenditure in the resting state, without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before initiation or resumption of sexual activity or therapy for sexual dysfunction.

5.4.4.2 *Intermediate- or indeterminate-risk category*

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

5.4.4.3 *High-risk category*

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. High-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

5.5 Diagnostic Evaluation (advanced work-up)

Most patients with ED can be managed based on the basis of medical and sexual history; conversely, some patients may need specific diagnostic tests (Tables 12 and 13).

5.5.1 ***Nocturnal penile tumescence and rigidity test***

The nocturnal penile tumescence and rigidity (NPTR) test applies nocturnal monitoring devices that measure the number of erectile episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erections. The NPTR assessment should be performed on at least two separate nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ≥ 10 minutes [443]. Nocturnal penile tumescence and rigidity monitoring is an attractive approach for objectively differentiating between organic and psychogenic ED (patients with psychogenic ED usually have normal findings in the NPTR test). However, many potential confounding factors (e.g., situational) may limit its routine use for diagnostic purposes [444].

5.5.2 ***Intracavernous injection test***

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernous injection and lasts for 30 minutes [445]. Overall, the test is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

5.5.3 ***Dynamic duplex ultrasound of the penis***

Dynamic duplex ultrasound (US) of the penis is a second-level diagnostic test that specifically studies the haemodynamic pathophysiology of erectile function. Therefore, in clinical practice, it is usually applied in those conditions in which a potential vasculogenic aetiology of ED (e.g., diabetes mellitus, renal transplantation, multiple concomitant CV risk factors and/or overt peripheral vascular disease, and poor responders to oral therapy) is suspected. Peak systolic blood flow > 30 cm/s, end-diastolic velocity < 3 cm/s and resistance index > 0.8 are considered normal [446, 447]. Recent data suggest that duplex scanning as a haemodynamic study may be better at tailoring therapy for ED, such as for low-intensity shock wave treatment (LI-SWT) and for diagnosing vasculogenic ED [448]. Further vascular investigation is unnecessary if a duplex US examination is normal.

5.5.4 ***Arteriography and dynamic infusion cavernosometry or cavernosography***

Pudendal arteriography should be performed only in patients who are being considered for penile revascularisation [449]. Recent studies have advocated the use of computed tomography (CT) angiography as a diagnostic procedure prior to penile artery angioplasty for patients with ED and isolated penile artery stenosis [450]. Nowadays, dynamic infusion cavernosometry or cavernosography are infrequently used tools for diagnosing venogenic ED.

5.5.5 *Psychopathological and psychosocial assessment*

Mental health issues and psychological distress are frequently comorbid with ED [451]. This is most evident for depression and anxiety related disorders, but may also include transitory states of altered mood (i.e., dysfunctional affective states resulting from a specific life stressor or crisis) [338, 452, 453]. Relationship factors, including lack of satisfaction with the partner, poor sexual relationships, length of the relationship, or feeling emotionally disconnected from the partner during sex, have been related to erectile difficulties and dysfunction [452, 454, 455]. In contrast, intimacy was found to be a protective factor in ED [329, 456]. Additionally, the cognitive factors underpinning organic and non-organic ED must also be assessed. Cognitive factors include male dysfunctional thinking styles and expectations about sexuality and sexual performance. These expectations result from the sexuality norms and stereotypes, shared by a given culture. Expectations emphasising high sexual performance in men, result in anxiety, which acts as a maintenance factor for ED [457, 458]. Unrealistic expectations about male sexual performance may further align with internal causal attributions regarding the loss of erection (i.e., men attribute the loss of erection to themselves [sense of personal inadequacy]), thereby worsening ED [457, 459]. Likewise, poor self-esteem and cognitive distraction from erotic cues, are expected to negatively affect ED [460, 461].

Psychosexual assessment in ED cases include a clinical interview considering all the previous topics. Clinicians are expected to collect information on the individual's psychopathological symptoms, life stressors, relationship dynamics, cognitive style, and cognitive distraction sources [460]. Also, self-reported measures are frequently used within the psychosocial context. These may include measurement scales such as the Brief Symptom Inventory [462] for measuring psychopathology symptoms, the Sexual Dysfunctional Beliefs Questionnaire [463] or the Sexual Modes Questionnaire [464] for measuring dysfunctional cognitive styles in men. It is worth noting that most literature follows a heteronormativity view. There is recent evidence suggesting that men who have sex with men present specific psychological risks associated with erectile capability regarding anal sex; minority stress, i.e. stress steaming from conflicting sexual identity, was associated with increased erectile difficulties in these men [465]. Therefore, professionals must tailor their assessment in the context of sexual minorities.

Figure 5: Psychopatholgical and psychosocial assessment

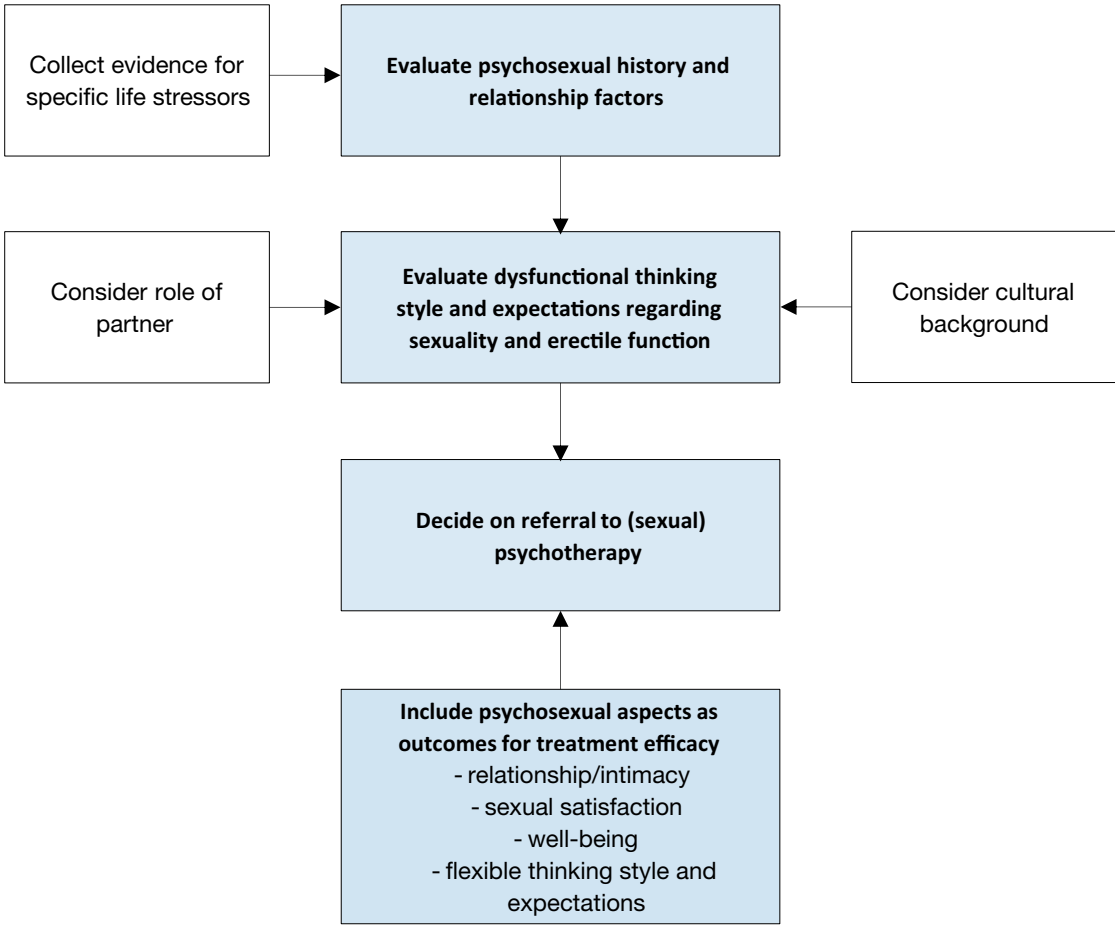

Collect evidence for specific life stressors
Evaluate psychosexual history and relationship factors
Consider role of partner
Evaluate dysfunctional thinking style and expectations regarding sexuality and erectile function
Consider cultural background
Decide on referral to (sexual) psychotherapy
Include psychosexual aspects as outcomes for treatment efficacy
- relationship/intimacy
- sexual satisfaction
- well-being
- flexible thinking style and expectations

Table 12: Indications for specific diagnostic tests for ED

Primary ED (not caused by acquired organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative
revascularisation surgery or angioplasty.
Patients with penile deformities that might require surgical correction (e.g., Peyronie's disease and congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end-stage ED, and sexual abuse).

Table 13: Specific diagnostic tests for ED

Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies - Intracavernous vasoactive drug injection - Penile dynamic duplex ultrasonography - Penile dynamic infusion cavernosometry and cavernosography - Internal pudendal arteriography
Specialised endocrinological studies
Specialised psycho-diagnostic evaluation

*5.5.6 **Recommendations for diagnostic evaluation of ED***

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 11.	Strong

5.6 Treatment of erectile dysfunction

*5.6.1 **Patient education - consultation and referrals***

Educational intervention is often the first approach to sexual complaints, and consists of informing patients about the psychological and physiological processes involved in the individual's sexual response, in ways the patient can understand. This first level approach has been shown to favour sexual satisfaction in men with ED [466]. Accordingly, consultation with the patient should include a discussion of the expectations and needs of the patient's and their sexual partner. It should also review the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rationale for treatment selection [467]. Patient and partner education is an essential part of ED management [467, 468], and may prevent misleading information that can be at the core of dysfunctional psychological processes underpinning ED.

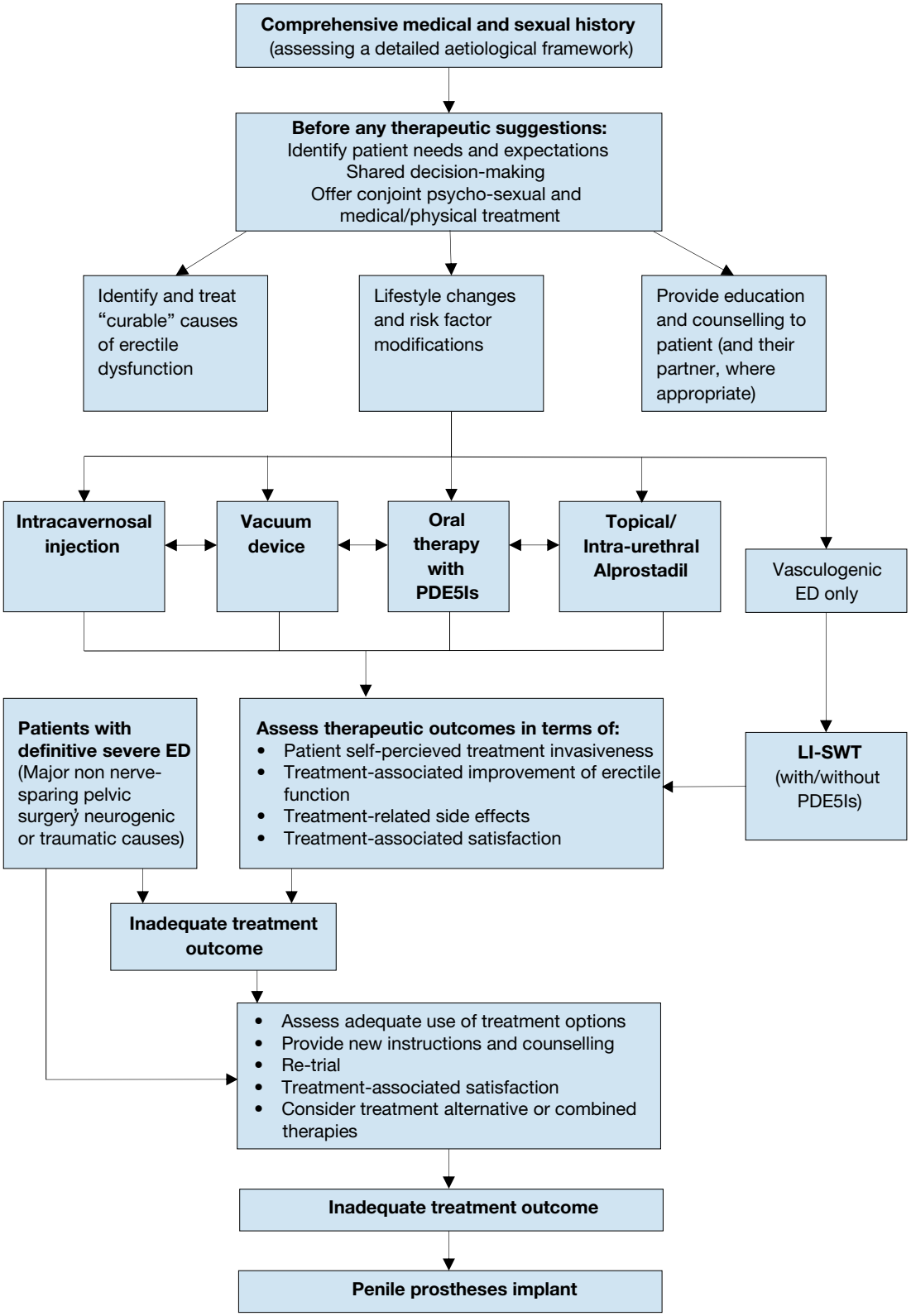
*5.6.2 **Treatment options***

Based on the currently available evidence and the consensus of the Panel, a novel comprehensive therapeutic and decision-making algorithm (Figure 6) for treating ED, which takes into account the level of invasiveness of each therapy and its efficacy, has been presented. This newly-developed treatment algorithm was extensively discussed within the guidelines panel as an alternative to the traditional three-level concept, to better tailor a personalised therapy to individual patients, according to invasiveness, tolerability and effectiveness of the different therapeutic options and patients' expectations. In this context, patients should be fully counselled with respect to all available treatment modalities.

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [377]. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (e.g., endocrine disorders and metabolic disorders such as diabetes, and some cardiovascular problems such as hypertension) which should always be well-controlled as the first step of any ED treatment [469]. Major clinical potential benefits of lifestyle changes may be achieved in men with specific co-morbid CV or metabolic disorders, such as diabetes or hypertension [377, 470].

As a rule, ED can be treated successfully with current treatment options, but it cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism) [53, 432], which potentially can be cured with specific treatments. Most men with ED are not treated with cause-specific therapeutic options. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety and cost, as well as patient preference [467]. In this context, physician-patient (partner, if available) dialogue is essential throughout the management of ED. Interesting insights come from a recent systematic review that showed a consistent discontinuation rate for all available treatment options (4.4-76% for PDE5Is); 18.6-79.9% for intracavernous injections; 32-69.2% for urethral suppositories; and 30% for penile prostheses). Men's beliefs about ED treatment, therapeutic ineffectiveness, adverse effects, quality of men's intimate relationships and treatment costs are the most prevalent barriers to treatment actual use [471].

Figure 6: Management algorithm for erectile dysfunction


Comprehensive medical and sexual history
(assessing a detailed aetiological framework)
Before any therapeutic suggestions:
Identify patient needs and expectations
Shared decision-making
Offer conjoint psycho-sexual and medical/physical treatment
Identify and treat "curable" causes of erectile dysfunction
Lifestyle changes and risk factor modifications
Provide education and counselling to patient (and their partner, where appropriate)
Intracavernosal injection
Vacuum device
Oral therapy with PDE5Is
Topical/ Intra-urethral Alprostadil
Vasculogenic ED only
Patients with definitive severe ED (Major non nerve-sparing pelvic surgery neurogenic or traumatic causes)
Assess therapeutic outcomes in terms of:
Patient self-percieved treatment invasiveness
Treatment-associated improvement of erectile function
Treatment-related side effects
Treatment-associated satisfaction
LI-SWT (with/without PDE5Is)
Inadequate treatment outcome
Assess adequate use of treatment options
Provide new instructions and counselling
Re-trial
Treatment-associated satisfaction
Consider treatment alternative or combined therapies
Inadequate treatment outcome
Penile prostheses implant

ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors; LI-SWT = low-intensity shockwave therapy.

5.6.2.1 Oral pharmacotherapy

Four potent selective PDE5Is have been approved by the EMA for treatment of ED [472]. Phosphodiesterase type 5 catalyses the hydrolysis of the second messenger cyclic guanosine monophosphate (cGMP) in the cavernous tissue; cGMP is involved in intra-cellular signalling pathways of cavernous smooth muscle. Accumulation of cGMP sets in motion a cascade of events at the intracellular level, which induces a loss of

contractile tone of the penile vessels by lowering cytosolic Ca^{2+}. Nitric oxide (NO) has an essential role in promoting the formation of cGMP and other pathways leading to corporeal smooth muscle relaxation and erection of the penis [469, 473]. This is associated with increased arterial blood flow, eventually leading to compression of the sub-tunical venous plexus followed by erection [474]. Since they are not initiators of erection, PDE5Is require sexual stimulation to facilitate an erection. Efficacy is defined as an erection, with rigidity, sufficient for satisfactory intercourse [469].

Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [475]. It is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and adverse effects [475]. Sildenafil is effective 30-60 minutes after administration [475]. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to 12 hours [476]. The pharmacokinetic profile for sildenafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited [477, 478]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% in a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [479]. Sildenafil significantly improved patient scores for IIEF, sexual encounter profile question 2 (SEP2), SEP question 3 (SEP3) and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established, irrespective of age [480]. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at a dose of 50 mg has been developed, mainly for patients who have difficulty swallowing solid dosage forms.

Tadalafil

Tadalafil was licensed for treatment of ED in February 2003 and is effective from 30 minutes after administration, with peak efficacy after about 2 hours [481]. Efficacy is maintained for up to 36 hours [481] and is not affected by food [482]. Usually, tadalafil is administered in on-demand doses of 10 and 20 mg or a daily dose of 5 mg. The recommended on-demand starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [481, 483]. Pharmacokinetic data for tadalafil are presented in Table 14. Adverse effects (Table 15) are generally mild in nature and self-limited by continuous use. In pre-marketing studies, after 12 weeks of treatment in a dose-response study, improved erections were reported by 67% and 81% of men with ED taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the placebo control group [481]. Tadalafil significantly improves patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction [481].

Efficacy of tadalafil has been confirmed in post-marketing studies [472, 484] and in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus) [485].

Tadalafil has also been shown to have a net clinical benefit in the short-term on ejaculatory and orgasmic functions in ED patients [486].

Daily tadalafil 5 mg has also been approved and licensed as a monotherapy in men with BPH-related LUTS, due to its ability to significantly improve urinary symptoms [487]. Therefore, its use may be considered in patients with ED patients also complaining of concomitant LUTS, and wishing to benefit from a single therapy [488]. Data have confirmed that 40% of men aged > 45 years were combined responders for ED and LUTS/BPH to treatment with tadalafil 5 mg once daily, with symptom improvement after 12 weeks [489]. To date, the main limitation on the use of daily tadalafil 5 mg as a combined therapy for both ED and LUTS is conditioned by the fact that no data are available in terms of efficacy and tolerability beyond 12 months of treatment.

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 minutes after administration [490], with one of three patients achieving satisfactory erections within 15 minutes of ingestion [491]. Its effect is reduced by a heavy, fatty meal. Doses of 5, 10 and 20 mg have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [492]. Pharmacokinetic data for vardenafil are presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited by continuous use [492]. After 12 weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of men with ED taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [492, 493]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction.

Efficacy has been confirmed in post-marketing studies [492, 493]. The efficacy of vardenafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. An orodispersable tablet (ODT) formulation of vardenafil has been released [493]. Orodispersable tablet formulations offer improved convenience over film-coated formulations and

may be preferred by patients. Absorption is unrelated to food intake and they exhibit better bio-availability compared to film-coated tablets [494]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [494-496].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [497]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes, ideally allowing for the drug to be used for ED while minimising adverse effects (although head-to-head comparisons are not yet available) [498]. Doses of 50, 100 and 200 mg have been approved for on-demand treatment of ED [497]. The recommended starting dose is 100 mg taken as needed 15-30 minutes before sexual activity and the dose may be adapted according to efficacy and tolerability [497, 499, 500]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58% and 59% for the 50, 100 and 200 mg groups, respectively, as compared with ~28% for placebo [497, 499]. Data from sexual attempts made within 15 minutes of treatment showed successful attempts in 64%, 67% and 71% of cases treated with avanafil 50, 100 and 200 mg, respectively. Dose adjustments are not warranted based on renal function, hepatic function, age or sex [499]. Pharmacokinetic data for avanafil are presented in Table 14 [497, 499]. Adverse effects are generally mild in nature (Table 15) [497, 499]. Pairwise meta-analytic data from available studies have suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3 and GAQ, with an evident dose-response relationship [497, 501]. Administration with food may delay the onset of effect compared with administration in a fasting state but avanafil can be taken with or without food [502]. The efficacy of avanafil in many groups of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus), has been successfully established. As for dosing, 36.4% (28 of 77) of sexual attempts (SEP3) at $\leq$ 15 minutes were successful with avanafil vs. 4.5% (2 of 44) after placebo ($P < 0.01$) [503]. A recent meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil [502].

Choice or preference among the different PDE5Is

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for the most-widely available PDE5Is (i.e., sildenafil, tadalafil, vardenafil, and avanafil). Choice of drug depends on frequency of intercourse (occasional use or regular therapy, 3-4 times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it. Two different network meta-analyses demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg and switch to Udenafil 100 mg if the treatment is not sufficient (however, Udenafil 100 mg is not EMA or US Food and Drug Administration approved and is not available in Europe) [484, 504]. The results of another clinical trial have revealed that tadalafil 5 mg once daily may improve erectile function among men who have a partial response to on-demand PDE5I therapy [505].

Continuous use of PDE5Is

From a pathophysiological standpoint, animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structural alterations caused by age, diabetes or surgical damage [506-510]. No data exist in humans. In humans, a RCT has shown that there is no clinically beneficial effect on endothelial dysfunction measured by flow-mediated dilation deriving from daily tadalafil when compared to placebo [511].

From a clinical standpoint, in 2007, tadalafil 2.5 and 5 mg/day were approved by the EMA for treatment of ED. According to the EMA, a once-daily regimen with tadalafil 2.5 or 5 mg might be considered suitable, based on patients' choice and physicians' judgement. In these patients, the recommended dose is 5 mg, taken once daily at approximately the same time. Overall, tadalafil, 5 mg once daily, provides an alternative to on-demand tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be linked. Overall, treatment with tadalafil 5 mg once daily in men complaining of ED of various severities is well-tolerated and effective [512].

An integrated analysis showed that, regardless of the type of ED population, there is no clinically significant difference between a tadalafil treatment administered with continuous (once daily) vs. on-demand regimen [511]. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [512, 513].

Table 14: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat ED*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C_{max}	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T_{max} (median)	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
T1/2	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
AUC	96%	94%	94%	99%
Protein binding	41%	NA	15%	8-10%
Bioavailability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics. C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination halftime; AUC = area under curve or serum concentration time curve.*

Table 15: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Safety issues for PDE5Is

(i) **Cardiovascular safety**

Clinical trial results for the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is has an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina [472, 514]. Chronic or on-demand use is well-tolerated with a similar safety profile. The prescription of all PDE5Is in patients with CVD or in those with high CV risk should be based on the recommendations of the 3rd Princeton Consensus Panel [440].

(ii) **Contraindication for the concomitant use of organic nitrates**

An absolute contraindication to PDE5Is is use of any form of organic nitrate (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donors (e.g., other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate such as “poppers” that are used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours if sildenafil (and probably also vardenafil) is used (half-life, 4 hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than 12 hours if avanafil is used (half-life, 6-17 hours) [515-518].

(iii) **Use caution with antihypertensive drugs**

Co-administration of PDE5Is with antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor [440]. In general, the adverse event profile of a PDE5I is not worsened by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents [519].

(iv) **Interaction with Nicorandil**

In vitro studies in animals suggest that the potassium channel opener nicorandil may potentiate the vasorelaxation induced by isoproterenol in isolated rat aorta by increasing cyclic GMP levels [520]. This may be due to the nitric oxide donating properties of nicorandil. Therefore, concurrent use of nicorandil and PDE5Is is also contraindicated.

α-Blocker interactions

Tadalafil 5 mg is currently the only licensed drug for the treatment of both ED and LUTS with level 1 evidence confirming its overall good efficacy in relieving urinary symptoms and improving erectile function [488]. As such, this treatment should be considered in patients suffering from mild to moderate LUTS associated with ED either alone or in combination with alpha-blockers. To this regard, given that both drugs are vasodilators with a potential risk of hypotension, historically there has always been caution in the combination of alpha-blockers and PDE5I (any) because of the fear of possible cumulative effects on blood pressure, based on the evidence from some individual studies that reported the tolerability of combination therapy [476, 491, 521]. However, a recent meta-analysis concluded that a concomitant treatment with α-blockers [both non-uroselective (e.g., terazosin and doxazosin) and uro-selective (e.g., alfuzosin, tamsulosin and silodosin) and PDE5Is may produce changes in haemodynamic parameters, but it does not increase the rate of adverse events due to hypotension [520]. Therefore, there is no current limitation in the simultaneous use of α-blockers and PDE5I, prioritising the use of uro-selective drugs in order to further minimise the risk of dizziness or other adverse events, thus including hypotension.

Dosage adjustment

Drugs that inhibit the CYP34A pathway inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (e.g., ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

Management of non-responders to PDE5Is

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy. Data suggest that an adequate trial involves at least six attempts with a particular drug [522]. The management of non-responders depends upon identifying the underlying cause [523].

Check that the medication has been properly prescribed and correctly used. The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The most common causes of incorrect drug use are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

Check that the patient has been using a licensed medication. There is a large counterfeit market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the medication is ineffective. Furthermore, the reduced production of NO that occurs in diabetic patients due to peripheral neuropathy, is thought to be the justification for the higher failure rate of PDE5Is in this category of patients. Oral PDE5Is take different times to reach maximal plasma concentrations (C_{max}) [476, 478, 494, 501, 524-526]. Although pharmacological activity is achieved at plasma levels below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of action in some patients within 15-30 minutes of oral ingestion [478, 494, 524-526], most patients require a longer delay between taking the medication [492, 501, 527, 528]. Absorption of both sildenafil and vardenafil can be delayed by a heavy, fatty meal [529]. Absorption of tadalafil is less affected, and food has negligible effects on its bioavailability [524]. When avanafil is taken with a high-fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (area under the curve). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [497, 498, 501].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is ~4 hours, suggesting that the normal window of efficacy is 6-8 hours following drug ingestion, although responses following this time period are recognised. The half-life of avanafil is 6-17 hours. Tadalafil has a longer half-life of ~17.5 hours, so the window of efficacy is longer at ~36 hours. Data from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I [523, 530-533]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I [523, 530, 531].

A systematic review has addressed the association between genetic polymorphism, especially those encoding endothelial nitric oxide synthase, and the variability in response to PDE5Is [534]. Similar recent data have suggested that response to sildenafil treatment is also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalysing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil [535-537].

Clinical strategies in patients correctly using a PDE5Is

Overall, treatment goals should be individualised to restore sexual satisfaction for patients and/or couples, and improve QoL based on patients' expressed needs and desires [538]. In this context, data suggests that almost half of patients abandon first-generation PDE5Is within 1 year, with no single specific factor playing a major role in dropout rates [539].

Uncontrolled trials have demonstrated that hypogonadal patients not responding to PDE5Is may improve their response to PDE5Is after initiating testosterone therapy [53, 469, 540]. Therefore, in the real-life setting most patients with ED will first be prescribed a PDE5I, which is usually effective; however, if diagnostic criteria suggestive for testosterone deficiency are present, testosterone therapy may be more appropriate even in ED patients [5, 53].

Modification of other risk factors may also be beneficial, as previously discussed. Limited data suggest that some patients might respond better to one PDE5I than to another [541], and although these differences might be explained by variations in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful. However it is important to emphasise that the few randomised studies have shown any difference in clinical outcomes with different drugs and intake patterns in patients with classic ED [542] and in special populations such as people with diabetics [543].

In refractory, complex, or difficult-to-treat cases of ED patients a combination therapy should be considered as a first-line approach. Although the available data are still limited, combining PDE5I with antioxidant agents, shockwave therapy or a vacuum erection device (VED) improves efficacy outcomes, without any significant increase in adverse events [544]. Similarly, the association of daily tadalafil with a short-acting PDE5I (such as sildenafil) leads to improved outcomes, without any significant increase in adverse effects [545].

5.6.2.2 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil can be administered intraurethrally with two different formulations. The first delivery method is topical, using a cream that includes a permeation enhancer to facilitate absorption of alprostadil (200 and 300 µg) via the urethral meatus [546, 547]. Clinical data are still limited. Significant improvement compared to placebo was recorded for IIEF-EF domain score, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [548]. Adverse effects include penile erythema, penile burning, and pain that usually resolve within 2 hours of application. Systemic adverse effects are rare. Topical alprostadil (VITAROS™) at a dose of 300 µg is available in some European countries. Recently, a randomised cross-over clinical trial has shown that, compared to the standard administration route, direct delivery within the urethral meatus can increase efficacy and confidence among patients, without increasing adverse effects [549].

The second delivery method is by intra-urethral insertion of a specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) [229]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, it is recommended that intra-urethral alprostadil is initiated at a dose of 500 µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regard to adverse events. In case of unsatisfactory clinical response, the dose can be increased to 1000 µg [550-552]. The application of a constriction ring at the root of the penis may improve efficacy [551, 552].

Overall, the most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration. Efficacy rates are significantly lower than for intracavernous pharmacotherapy [553], with ~30% adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

5.6.2.3 Shockwave therapy

The use of LI-SWT has been increasingly proposed as a treatment for vasculogenic ED over the last decade, being the only currently marketed treatment that might offer a cure, which is the most desired outcome for most men suffering from ED [448, 554-561].

Overall, several single-arm trials have shown a beneficial effect of LI-SWT on patient-reported erectile function, but data from prospective randomised trials are conflicting, and many questions remain to be answered especially because of the heterogeneity among shockwave generators (i.e., electrohydraulic,

electromagnetic, piezoelectric and electropneumatic); type of shockwaves delivered (i.e., focused, linear, semi-focused and unfocused); set-up parameters (e.g., energy flux density and number of pulses per session) and treatment protocols (i.e., duration of treatment, number of sessions per week, total number of shockwave pulses delivered and penile sites of application) [562, 563]. In a recent trial trying to assess the best treatment parameters, no significant differences were observed between various energy flux density levels although a 0.10 mJ/mm^2 seems to perform slightly better than lower energies [564]. Most of the studies have suggested that LI-SWT can significantly increase the IIEF and EHS in patients with mild vasculogenic ED, although this improvement appears modest and the rates of patients reporting a satisfactory improvement range between 40-80% [448, 562]. Few studies have shown an improvement in penile haemodynamic parameters after LI-SWT, but the clinical meaning of this improvement remains unclear [562, 565]. Likewise, data suggest that LI-SWT could ameliorate erection quality even in patients with severe ED who are either PDE5Is non-responders [559, 566, 567] or inadequate responders [568], thus reducing the immediate need for more invasive treatments. Treatment effect appears to be clinically evident starting from 1-3 months after treatment completion, with a subsequent progressive decrease of the achieved benefit in terms of erectile function over time, although some effects could be still detected up to 5 years after treatment [562, 564, 569]. Recently, the impact of LI-SWT has been also tested in the setting of penile rehabilitation after radical prostatectomy in 2 small, randomised trials showing only modest advantage compared to conventional PDE5is [570, 571].

Overall, larger prospective RCTs and longer-term follow-up data are necessary to provide clinicians with more confidence regarding the use and effectiveness of LI-SWT for ED. Further clarity is also needed in defining treatment protocols that can result in greater clinical benefits [572, 573].

As a whole, according to the available data and the novel treatment decision algorithm, LI-SWT may be offered to patients with vasculogenic ED, although they should be fully counselled before treatment.

5.6.2.4 Psychosocial intervention and therapy

Psychosocial interventions including different modalities (e.g., sexual skills training, marital therapy, psychosexual education) [466], and Cognitive and Behavioural Therapy (CBT - group or couple format), are recommended [460]. Cognitive and Behaviour Therapy is aimed at altering dysfunctional cognitive and behavioural patterns influencing ED, and increasing adjustment during the course of the disorder. Some of its techniques include identifying triggers preceding erectile difficulties, cognitive restructuring of dysfunctional thinking styles, learning coping skills aimed at dealing with erectile difficulties and emotional symptoms, improving communications skills with the partner, and relapse prevention. The CBT approach combined with medical treatment for ED has received empirical support and is considered an optimal procedure [574]. Moreover, there is preliminary evidence supporting the role of mindfulness-based therapy for ED and associated outcomes such as sexual satisfaction [575].

5.6.2.5 Hormonal treatment

The advice of an endocrinologist should be sought for managing patients with certain hormonal abnormalities or endocrinopathies [432]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g., a functional pituitary tumour resulting in hyperprolactinaemia) [432, 576]. When clinically indicated [577], testosterone therapy (intramuscular, transdermal, or oral) can be considered for men with low or low-normal testosterone levels and concomitant problems with their sexual desire, erectile function and dissatisfaction derived from intercourse and overall sex life (see Section 3.6 for a comprehensive discussion of testosterone therapy).

5.6.2.6 Vacuum erection devices

Vacuum erection devices (VED) provide passive engorgement of the corpus cavernosum, together with a constrictor ring placed at the base of the penis to retain blood within the corpus. Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% [578, 579]. Most men who discontinue use of VEDs do so within 3 months. Long-term use of VEDs decreases to 50-64% after 2 years [580]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness [579]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy [581, 582]. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED [578, 579, 583].

5.6.2.7 Intracavernous injections therapy

Intracavernous administration of vasoactive drugs was the first medical treatment introduced for ED [533, 584]. According to invasiveness, tolerability, effectiveness and patients' expectations (Figure 6), patients may be offered intracavernous injections. The success rate is high (85%) [553, 585].

5.6.2.7.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [533, 586]. Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5-40 µg (40 µg may be offered off label in some European countries). The erection appears after 5-15 minutes and lasts according to the dose injected, but with significant heterogeneity among patients. An office-training programme is required for patients to learn the injection technique. In men with limited manual dexterity, the technique may be taught to their partners. The use of an automatic pen that avoids a view of the needle may be useful to resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., men with diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections [533, 584]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively-prolonged undesired erections (5%), priapism (1%), and fibrosis (2%) [533, 584, 587]. Pain is usually self-limited after prolonged use and it can be alleviated with the addition of sodium bicarbonate or local anaesthesia [533, 584, 588]. Cavernosal fibrosis (from a small haematoma) usually clears within a few months after temporary discontinuation of the injection programme. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernous injections indefinitely. Systemic adverse effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been reported for intracavernous pharmacotherapy [533, 584, 589, 590], with most drop-outs occurring within the first 2-3 three months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year [591]. Reasons for discontinuation included desire for a permanent mode of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up are important in addressing patient withdrawal from an intracavernous injection programme [592-594].

5.6.2.7.2 Combination therapy

Table 16 details the available intracavernous injection therapies (compounds and characteristics). Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating adverse effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy because of its high incidence of adverse effects as monotherapy. Papaverine is currently not licensed for treatment of ED.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide, usually combined with the main drugs [595, 596]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Bimix, Trimix: papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg) (also known as Bimix), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg) (also known as Trimix), have been widely used with improved efficacy rates, although they have never been licensed for ED [597, 598]. Trimix has the highest efficacy rates, reaching 92%; this combination has similar adverse effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on total dose).
- Invicorp™: Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp), currently licensed in Scandinavia, is a combination of two active components with complementary modes of action. Clinical studies have shown that the combination is effective for intracavernous injections in > 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernous therapies, is associated with a low incidence of penile pain and a virtually negligible risk of priapism [599].

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone [600]. However, combination therapy is associated with an increased incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant.

Table 16: Intracavernous injection therapy - compounds and characteristics

Name	Substance	Dosage	Efficacy	Adverse Events	Comment
Caverject™ or Edex/Viridal™	Alprostadil	5-40 µg/mL	~ 70%	Penile pain, priapism, fibrosis	Easily available
Papaverine	Papaverine	20 - 80 mg	< 55%	Elevation of liver enzymes, priapism, fibrosis	Abandoned as monotherapy
Phentolamine	Phentolamine	0.5 mg/mL	Poor efficacy as monotherapy	Systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Bimix	Papaverine + Phentolamine	30 mg/mL + 0.5 mg/mL	~ 90%	Similar to Alprostadil (less pain)	Not licensed for the treatment of ED
Trimix	Papaverine + Phentolamine + Alprostadil	30 mg/mL + 1 mg/mL + 10 µg/mL	~ 92%	Similar as Alprostadil (less pain)	Not licensed for the treatment of ED
Invicorp™	Vasoactive intestinal peptide (VIP) + Phentolamine	25 µg + 1-2 mg	~ 80%	Similar as Alprostadil without pain	Easily available

There are currently several potential novel treatment modalities for ED, from innovative vasoactive agents and trophic factors to stem cell therapy and gene therapy. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies to achieve adequate evidence-based and clinically-reliable recommendation grades [601-606]. A recent systematic review has concluded that five completed human clinical trials have shown promise for stem cell therapy as a restorative treatment for ED [607].

5.6.2.8 Other treatments

5.6.2.8.1 Platelet-Rich Plasma

The interest toward regenerative medicine for ED has significantly increased in the last decade [608]. Among these, intracavernous injection of platelet-rich plasma (PRP) has been recently investigated in several prospective and retrospective trials [609-615]. Platelet-rich plasma is obtained by centrifugation of patient autologous blood with subsequent extraction of a plasma fraction containing 3-7 times mean platelet concentration compared to the whole blood. The regenerative effect of PRP is deemed to be exerted through the high concentrations of platelets containing several growth factors including VEGF, EGF, IGF-1, PDGF and FGF [616]. These factors may be responsible for angiogenesis stimulation and stem cell recruitment [616]. Pre-clinical studies have shown a neuro-regenerative effect and an improved penile vascularisation in both cavernous nerve injury and diabetic rat-model [617]. In the clinical setting, the use of PRP has been previously investigated in the field of orthopaedics, plastic surgery and dermatology. To date, one randomised placebo controlled-trial [615], two prospective randomised trials [611, 612], two prospective cohort [609, 614] and two retrospective studies [610, 613] investigated the effect of intracavernous injection of PRP for ED. Overall, available findings demonstrate favourable outcomes of PRP injections in terms of IIEF-5 and SEP scores and peak systolic velocity on penile-duplex ultrasound [617]. In the only randomised placebo-controlled trial, 60 patients with mild to moderate vasculogenic ED were randomised to receive two injections of 10 mL PRP (n=30) or placebo (n=30) [615]. At 1, 3 and 6-month follow-up, the rate of patients reporting an MCID improvement in the IIEF-EF score was significantly higher in the treatment group, with 69% achieving minimal clinically important differences (MCID) 6 months after PRP compared to 27% in the placebo group ($p < 0.001$). IIEF-EF scores improved by a mean of 2.7 points at 1-month and 3.9 points at 6-month assessment after treatment. Regarding safety, the mean VAS score was higher as compared with placebo (2.6 vs. 2.2, respectively, $p = 0.008$) but no haemorrhagic events or other side effects were reported [615]. Despite these encouraging results, the available evidence is still insufficient to provide a recommendation regarding the use of PRP for ED treatment in clinical practice. Indeed, current studies are limited by the low number of patients included (ranging from 10-100), the lack of placebo comparison (except for 1 small RCT) and the heterogeneity in terms of the modality of PRP preparation. The concentration of platelets and growth factors could vary

according to the system used for preparation [618] and there is a lack of consensus concerning the optimal platelet concentration as well as the need for combining PRP with activating agents such as $CaCl_2$ or thrombin to maximise the growth factors release [617, 618]. Intracavernous injection of PRP should be used only in a clinical trial setting.

5.6.2.8.2 Herbal medicine and natural supplements

In recent years there has been an exponential growth in the market of medicinal herbs and natural supplements for the treatment of ED, but with very little available evidence of robust scientific data to support their efficacy and safety. Recently, a Cochrane review showed that ginseng may only have trivial effects on erectile function or satisfaction with intercourse compared to placebo when assessed using validated tools [619]. Moreover, data suggested that daily administration of oral L-arginine, only when in combination with PDE5I use, improves sexual function [620].

5.6.2.9 Erectile dysfunction after radical prostatectomy

Use of pro-erectile drugs following RP is important in achieving post-operative erectile function and to allow patients to resume sexual activity. There is also some evidence in animal studies that this may avoid cavernous fibrosis and maintain penile length. Several trials have shown improvements in erectile function after RP in patients receiving drugs (any therapeutic or prophylactic) for ED. Early compared with delayed erectile function treatment affects the natural recovery time for potency [621], although there is a lack of data to support any specific regimen, which is either optimal for penile rehabilitation or may result in the achievement of spontaneous, non-pharmacologically assisted erections [390, 622, 623]. In prospective studies, there has been no evidence that penile rehabilitation itself increases the chances of spontaneous recovery of erectile function in men following nerve-sparing RP (NSRP) [623]. The currently available therapeutic armamentarium follows the treatment algorithm for ED, which is shown in Figure 4.

Management of post-RP ED has been revolutionised by the advent of PDE5Is, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. In this context, it must be emphasised that post-RP, ED patients are poor responders to PDE5Is. Since their launch on the market, PDE5Is have been considered as the first-line therapy in patients who have undergone NS surgery, regardless of the surgical technique used [390, 400]. Several clinical parameters have been identified as potential predictors of PDE5Is outcomes in men undergoing RP. Patient age, baseline erectile function, and quality of NS technique are key factors in preserving post-RP erectile function [400, 409, 624].

The response rate to sildenafil treatment for ED after RP in different trials has ranged from 35-75% among those who underwent NSRP and from 0-15% among those who underwent non-NSRP [400, 625]. Early use of high-dose sildenafil after RP is associated with preservation of smooth muscle within the corpus cavernosum [626]. A single study demonstrated that daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [627]. Conversely, a more recent prospective, randomised, placebo-controlled study, which assessed the effects of nightly sildenafil citrate therapy during penile rehabilitation using nocturnal penile rigidity score in addition to the IIEF-EF domain showed no therapeutic benefit for nightly sildenafil when compared to on-demand dosing in recovery of erectile function post-prostatectomy [628].

A large multicentre trial in Europe and the USA investigated the effects of tadalafil in patients with ED following bilateral NSRP. Erectile function was improved in 71% of patients treated with 20 mg tadalafil versus 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil vs. 26% with placebo [629]. Moreover, a randomised, double-blind, double-placebo trial in men < 68 years of age and with normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [623]. Tadalafil was most effective for drug-assisted erectile function in men with ED following NSRP and data suggested a potential role for tadalafil once daily (provided early after surgery) in contributing to the recovery of post-operative erectile function and maintaining penile length [623]. Conversely, unassisted or spontaneous recovery of erectile function was not improved after cessation of active therapy for 9 months [623]. However, tadalafil once daily improved QoL post-operatively, both at double-blind and open label treatment periods [630].

Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study [631]. Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [632]. A randomised, double-blind, double-dummy,

multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP [622]. In patients whose pre-operative erectile function domain score was > 26, vardenafil was efficacious when used on demand [622].

A double-blind, placebo-controlled, parallel-group study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (30 minutes before sexual activity) for 12 weeks showed significantly greater increases in SEP2 and SEP3 as well as in mean change of IIEF erectile function domain score with 100 and 200 mg avanafil versus placebo ($P < 0.01$) [442].

A recent Cochrane review analysed data from eight RCTs [633]. It showed that scheduled PDE5I may have little or no effect on short-term (up to 12 months) self-reported potency when compared to placebo or no treatment. In this study, daily PDE5I made little to no difference in short- and long-term erectile function. The authors conclude that penile rehabilitation strategies using PDE5I following RP do not increase self-reported potency and erectile function compared to on-demand use. Therefore, daily PDE5Is result in little to no difference in both short- and long-term (> 12 months) self-reported potency when compared to scheduled use. Finally, at short-term follow-up, daily PDE5I may result in little or no effect on self-reported potency when compared to scheduled intra-urethral application of prostaglandin E1.

Historically, the treatment options for post-RP ED have included intracavernous injections [634], urethral micro-suppository [400, 635], VED [390, 400, 636, 637], and penile implants [400, 638, 639]. Intracavernous injections and penile implants had been suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or not suitable for post-operative patients [390, 640]. A meta-analysis had shown that the early use of VED has an excellent therapeutic effect on post-RP patients and no serious adverse effects, therefore it should be considered as a therapeutic alternative [641]. Recent findings from two network meta-analyses show that: i) Sildenafil 100 mg regular dose (once daily or nightly) is the optimum penile rehabilitation strategy to improve erectile function recovery rates after RP, while the on-demand dose of PDE5Is should not be considered and recommended as a penile rehabilitation strategy [642]; ii) the combination therapy with VED and PDE5is offers clear advantages over monotherapy, thus this combined approach should be considered in the clinical management of penile rehabilitation after RP [643].

Findings from a systematic review had suggested that pelvic floor muscle training (PFMT) combined with bio-feedback is a promising alternative to pharmacological treatments, although there is a need for future well-powered, rigorously designed RCTs to draw strong conclusions [644].

5.6.2.10 Surgical management

5.6.2.10.1 Surgery for post-traumatic arteriogenic ED

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [582, 645]. The stenosis must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography.

5.6.2.10.2 Venous ligation surgery

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [645].

5.6.2.10.3 Penile prostheses

The surgical implantation of a penile prosthesis may be considered in patients who i) are not suitable for different pharmacotherapies or prefer a definitive therapy; and, ii) do not respond to pharmacological therapies (Figure 6) [646]. A systematic review addressing cause and duration of symptoms before implantation has shown that most men receiving a penile prosthesis have an organic cause of ED, with vascular disease, diabetes, and previous pelvic surgery/trauma being the most common [647]. Similar findings have been reported by a prospective registry of penile prostheses with > 3-year collection period in the UK; the three commonest aetiological factors for ED were diabetes, prostate surgery and Peyronie's disease [648]. The mean duration of ED symptoms before surgical intervention ranges from 3-6 six years [647].

The two currently available classes of penile implants include inflatable (two- and three-piece) and semi-rigid devices (malleable, mechanical and soft flexible) [400, 638, 649-651]. Patients may prefer the three-piece inflatable devices due to the more "natural" erections obtained, although no prospective RCTs have compared satisfaction rates with both types of implants. The two-piece inflatable prosthesis can be a viable option among patients who are deemed at high-risk of complications with reservoir placements (e.g., previous abdominal

surgery). Semi-rigid prostheses result in a firm penis, which may be manually placed in an erect or flaccid state and offer the advantage of a simple implant technique, as well as easy use for the patient [400, 638, 649, 650]. Conversely, they can have the disadvantage of unnatural persistent erection and reduced concealability [650, 652]. They may also be an option in men with limited manual dexterity.

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic [649, 650, 652, 653]. The peno-scrotal approach has been suggested to provide an excellent exposure; afford proximal crural exposure, avoid dorsal nerve injury, and permit direct visualisation of pump placement. However, with this approach, the reservoir is either placed blindly into the retropubic space, which can result in visceral injury in patients with a history of major pelvic surgery (mainly radical cystectomy) or a separate incision in the abdomen is placed under direct vision. A recent systematic review comparing the satisfaction and complication rates of the different surgical approaches has shown that there is no specific advantage between the two, but rather it is recommended that surgeons have knowledge of both techniques and are capable of tailoring the incision strategy for complex cases [654]. Revision surgery is associated with poorer outcomes and may be more challenging. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED with appropriate counselling [400, 638, 649, 655-663]. In patients with favourable oncological prognosis after RP for PCa, a contemporary surgery to treat both ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established and definitive role to address both problems [400, 638, 664-666]. Structured psychosexual counselling may improve sexuality and sexual well-being in both patients and their partners after penile implant surgery [667].

5.6.2.10.4 Penile prostheses implantation: complications

Historically, the two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prostheses (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in mechanical failure rates of < 5% after 5 years of follow-up [638, 668, 669]. Careful surgical techniques with appropriate antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduced infection rates to 2-3% with primary implantation in low-risk patients and in high-volume centres, although the definition of a high-volume centre still needs clarification [670-673]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [638, 670, 674-677]. Methods that decrease infections include using coated prostheses and strictly adhering to surgical techniques that avoid prolonged wound exposure and skin contact minimisation (i.e., no-touch technique).

Techniques that might prevent penile prostheses infection but lack definitive evidence include the use of prolonged post-operative antibiotics (> 24 hours), shaving with clippers, and preparation with chlorhexidine-alcohol [678, 679]. Identification and pre-treatment of patients who are colonised with nasal *Staphylococcus aureus* with mupirocin and chlorhexidine prior to surgery has been shown to reduce the incidence of post-operative surgical site infection from 4.4% to 0.9% in a placebo-controlled randomised trial [680]. On the whole, growing evidence suggests that the risk of penile prosthesis infection has reduced over the last few decades with device improvement and surgical expertise [681].

Higher-risk populations include patients undergoing revision surgery, those with impaired host defences (immunosuppression, diabetes mellitus, or spinal cord injury) or those with penile corporal fibrosis [638, 649, 671, 682-684]. A recent large database-study has shown that diabetes mellitus is a risk factor for penile prostheses infection, highlighting the need for optimal patient selection other than raising the question of whether lowering this risk by optimising glycaemic control before surgery [685]. Unfortunately, there are no RCTs determining the ideal and/or correct threshold of glycated haemoglobin that is acceptable prior to implant surgery in diabetic patients [686]. Recently, a large-cohort, multicentre, retrospective analysis in men with diabetes who received a Coloplast Titan™ implant demonstrated that vancomycin + gentamicin was the most efficacious combination of antibiotics used for implants dipping in terms of preventing postoperative infection and subsequent explantation and revision [687, 688].

Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate salvage and replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases [671, 683, 689, 690]. An absolute recommendation on how to proceed after explantation in this setting cannot be given and must be focused on the pros and cons of salvage therapy after full consultation with the patient. The majority of revisions are secondary to mechanical failure and combined erosion or infection [676, 678]. Ninety-three percent of cases are successfully revised, providing functioning penile prosthesis [671, 676, 689, 691, 692].

Besides infection and mechanical failure, impending erosion involving the distal corpora, urethra, glans or other structures can occur in 1-6% of cases after surgery [693]. Similarly, glans ischaemia and necrosis have been reported in about 1.5% of patients [693, 694]. Risk factors for these serious complications are higher in those patients with significant vascular impairment, such as patients with diabetes, or who have undergone concomitant lengthening procedures. Therefore, performing dual procedures at the time of implantation should be limited to mitigate the risks of serious complications.

5.6.2.10.5 Conclusions about penile prostheses implantation

Penile implants are an effective solution, usually for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rate [695]. There are also currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another [696].

Table 17: Penile prostheses models available on the market

Semi-rigid prostheses	**Inflatable prostheses**	
	Two-piece	**Three-piece**
AMS Tactra™ [Boston Scientific]	AMS Ambicor™ [Boston Scientific]	Titan™ [Coloplast]
Genesis™ [Coloplast]		Titan OTR NB™ (Narrow base) [Coloplast]
		Titan Zero Degree™
Tube™ [Promedon]		AMS 700 CX™ [Boston Scientific]
ZSI 100™ [Zephyr]		AMS 700 LGX™ [Boston Scientific]
Virilis II™ [Subrini]		AMS 700 CXR™ [Boston Scientific]
		ZSI 475™ [Zephyr]

5.6.3 Recommendations for treatment of ED

Recommendations	**Strength rating**
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to phosphodiesterase type 5 inhibitors (PDE5Is).	Weak
Use Cognitive Behaviour Therapy as a psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than erectile dysfunction (ED), including libido reduction, changes in orgasm, anejaculation, Peyronie's like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to, or at the same time, as initiating ED treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use PDE5Is as first-line therapeutic option.	Strong
Use topical/intra-urethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy.	Weak
Use topical/Intra-urethral alprostadil as an alternative first-line therapy, in well-informed patients, who do not wish to have intracavernous injections or in patients who prefer a less-invasive therapy.	Weak
Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices as first-line therapy in well-informed patients with infrequent sexual intercourse and co-morbidity requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Do not use platelet-rich plasma to treat ED outside the confines of a clinical trial.	Weak
Use implantation of a penile prosthesis if other treatments fail or depending upon patient preference.	Strong

Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/ pelvic surgery and other curative treatments for prostate cancer.	Weak

*5.6.4 **Follow-up***

Follow-up is important in order to assess efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

6. DISORDERS OF EJACULATION

6.1 Introduction

Ejaculation is a complex physiological process that comprises emission and expulsion processes and is mediated by interwoven neurological and hormonal pathways [697]. Any interference with those pathways may cause a wide range of ejaculatory disorders (Table 18).

Table 18: Spectrum of ejaculation disorders

Premature ejaculation
Retarded or delayed ejaculation
Anejaculation
Painful ejaculation
Retrograde ejaculation
Anorgasmia
Haemospermia

6.2 Premature ejaculation

*6.2.1 **Epidemiology***

Historically, the main problem in assessing the prevalence of PE has been the lack of a universally recognised definition at the time that surveys were conducted [192]. See Section 4.2 for a comprehensive discussion about epidemiology of PE.

*6.2.2 **Pathophysiology and risk factors***

The aetiology of PE is unknown, with few data to support suggested biological and psychological hypotheses, including anxiety [698-702], penile hypersensitivity [703-709] and 5-hydroxytryptamine (HT) receptor dysfunction [710-715]. The classification of PE into four subtypes [201] has contributed to a better delineation of lifelong, acquired, variable and subjective PE [716-718]. It has been hypothesised that the pathophysiology of lifelong PE is mediated by a complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors [719]. Acquired PE may occur due to psychological problems - such as sexual performance anxiety, and psychological or relationship problems - and/or co-morbidity, including ED, prostatitis and hyperthyroidism [720-722].

A significant proportion of men with ED also experience PE [209, 373]. High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED. According to the National Health and Social Life Survey (NHSLS), the prevalence of PE is not affected by age [197], unlike ED, which increases with age. Conversely, other data depicted an increased prevalence with ageing [702]; for instance, Verze *et al.* reported that PE prevalence based on the Premature Ejaculation Diagnostic Tool (PEDT) score (≥ 11) [723] proportionally increased with age [724]. Similarly, in a recent systematic review, PE was found to be more common in older age, with peak prevalence in men aged 60-69 years [725]. Premature ejaculation is not affected by marital or income status [197, 724]. However, PE is more common in Black men, Hispanic men, and men from regions where an Islamic background is common [196, 726] and prevalence may be higher in men with a lower educational level [197, 209]. Other risk factors include genetic predisposition [715, 727-730], poor overall health status and obesity [197], prostate inflammation [353, 731-734], hyperthyroidism [720], low prolactin levels [735], high testosterone levels [736], vitamin D and B12 deficiency [737, 738], diabetes [739,

740], MetS [741, 742], lack of physical activity [743], emotional problems and stress [197, 744, 745], depressive symptoms [745], and traumatic sexual experiences [197, 209]. In the only published study on risk modification/ prevention strategies [746], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in intravaginal ejaculatory latency time (IELT) and ejaculatory control compared to untreated patients.

*6.2.3 **Impact of PE on quality of life***

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less-frequent intercourse [284, 747, 748]. However, the negative impact of PE extends beyond sexual dysfunction. Premature ejaculation can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [284, 749, 750]. Moreover, PE may also affect the partner's sexual functioning and their satisfaction with the sexual relationship decreases with increasing severity of the patient's condition [751-753]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the Global Study of Sexual Attitudes and Behaviors survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [209], with men more likely to seek treatment for ED than for PE [209]. In the Premature Ejaculation Prevalence and Attitudes (PEPA) survey, only 9% of men with self-reported PE consulted a physician [198]. The main reasons for not discussing PE with their physician are embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE [754, 755]. Physicians need to encourage their patients to talk about PE.

*6.2.4 **Classification***

There is still little consensus about the definition and classification of PE [756]. It is now universally accepted that "premature ejaculation" is a broad term that includes several concepts belonging to the common category of PE. The most recent definition comes from the International Classification of Diseases 11th Revision, where PE was renamed as Early Ejaculation [757]: "Male early ejaculation is characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period of at least several months and is associated with clinically significant distress."

This definition includes four categories: male early ejaculation, lifelong generalised and situational, acquired generalised and situational, unspecified.

In the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), PE is defined as a sexual disorder with:

- consistent ejaculation within 1 minute or less of vaginal penetration;
- over a period of at least 6 months;
- experienced 75–100% of the time;
- the condition results in clinically significant distress, sexual frustration, dissatisfaction, or tension between partners;
- this condition is not better accounted for by another non-sexual mental disorder, medication or illicit substance use, or medical condition [216].

The EAU Guidelines have adopted the definition of PE that was developed by the International Society for Sexual Medicine as the first evidence-based definition [758]. According to this definition, PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

- ejaculation that always or nearly always occurs prior to or within about 1 minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE);
- inability to delay ejaculation on all or nearly all vaginal penetrations;
- negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

Two more PE syndromes have been proposed [717]:

- 'Variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Subjective PE' is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology.

The addition of these new syndrome types may help in overcoming the limitations of each individual definition and it may support a more flexible view of PE for patient stratification, diagnosis and treatment [759].

*6.2.5 **Diagnostic evaluation***

Diagnosis of PE is based on the patient's medical and sexual history [205, 760, 761]. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED. Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection [373, 762]. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [763]. There are several overlapping definitions of PE, with four shared factors (Table 19), resulting in a multi-dimensional diagnosis [764].

Table 19: Common factors in different definitions of PE

Time to ejaculation assessed by IELT
Perceived control
Distress, bother, frustration, interpersonal difficulty related to the ejaculatory dysfunction

6.2.5.1 Intravaginal ejaculatory latency time (IELT)

Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [765, 766], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [767, 768]. Moreover, some men may experience PE in their non-coital sexual activities (e.g., during masturbation, oral sex or anal intercourse) thus measuring IELT will not be suitable for their assessment. Intravaginal ejaculatory latency time has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse [747]. In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation) [769]. In everyday clinical practice, self-estimated IELT is sufficient [193]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [770]. Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) scale on control over ejaculation and satisfaction with sexual intercourse (0 = very poor, to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all, to 4 = extremely). However, self-estimated IELT may be over-estimated by ~1 minute and therefore it must be carefully substituted with stopwatch-measured IELT while identifying men with the complaint of lifelong PE in a clinical setting [771].

Measurement of IELT with a calibrated stopwatch is mandatory in clinical trials. For any drug treatment study of PE, Waldinger *et al.* suggested using geometric mean instead of arithmetic mean IELT because the distributed IELT data are skewed. Otherwise, any treatment-related ejaculation delay may be overestimated if the arithmetic mean IELT is used instead of the geometric mean IELT [772].

6.2.5.2 Premature ejaculation assessment questionnaires

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): A five-item questionnaire based on focus groups and interviews from the USA, Germany, and Spain assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [773]. A total score > 11 suggests a diagnosis of PE, 9 or 10 suggests a probable diagnosis of PE, and < 8 indicates a low likelihood of PE.

- Arabic Index of Premature Ejaculation (AIPE): A seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction of the patient and partner, anxiety or depression [774]. A cut-off score of 30 (range 7-35) discriminates PE diagnosis best. Severity of PE is classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

Although it is widely used, some studies have reported a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. Only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [301]. On the contrary, a recent study has shown that PEDT is valid in screening the presence of evidence-based-defined lifelong PE and acquired PE [62]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [770].

Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [768], Index of Premature Ejaculation (IPE) [775] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [776]. Currently, their role is optional in everyday clinical practice.

6.2.5.3 Physical examination and investigations

Physical examination may be part of the initial assessment of men with PE. It may include a focused examination of the urological, endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended [760].

6.2.5.4 Recommendations for the diagnostic evaluation of PE

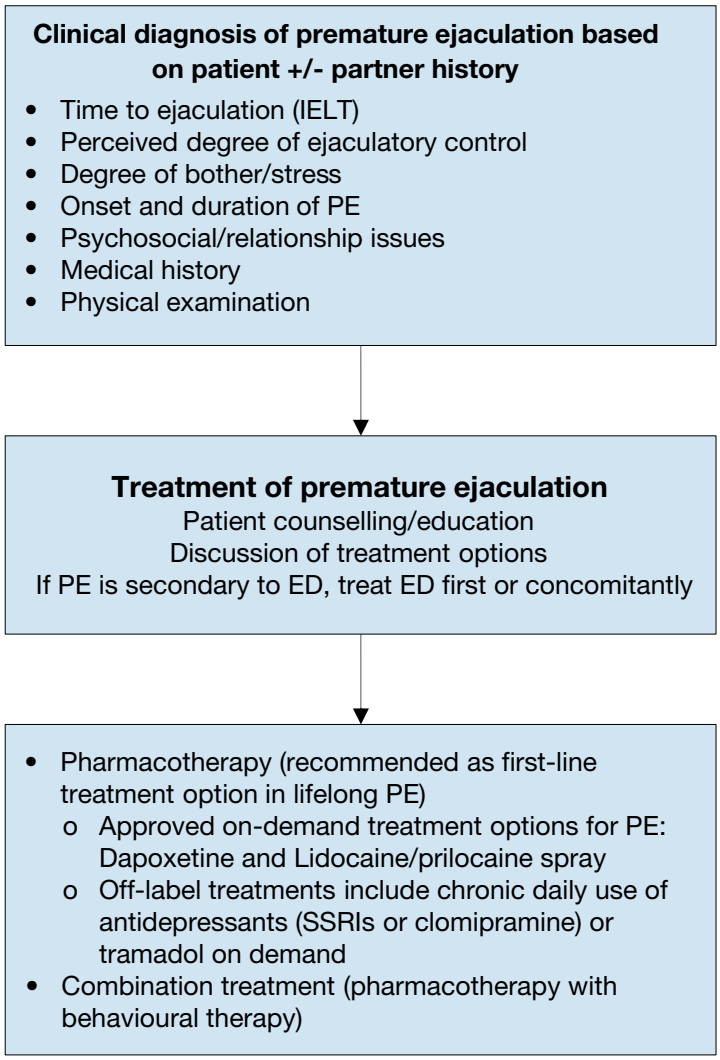
Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong
Use of stopwatch-measured IELT is not compulsory in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

*6.2.6 **Disease management***

Before commencing any treatment, it is essential to define the subtype of PE and discuss patient's expectations thoroughly. Pharmacotherapy must be considered as the first-line treatment for patients with lifelong PE, whereas treating the underlying cause (e.g., ED, prostatitis, LUTS, anxiety and hyperthyroidism) must be the initial goal for patients with acquired PE [205]. Various behavioural techniques may be beneficial in treating variable and subjective PE [777]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [778, 779]. However, there is weak and inconsistent evidence regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown [780].

In lifelong PE, behavioural techniques are not recommended alone, and pharmacotherapy must be considered as the basis of treatment [205]. Dapoxetine (30 and 60 mg) is the first on-demand oral pharmacological agent approved for lifelong and acquired PE in many countries, except for the USA [781]. The metered-dose aerosol spray of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) combination is the first topical formulation to be officially approved for on-demand treatment of lifelong PE by the EMA in the European Union [782]. All other medications used in PE are off-label indications [775]. Daily or on-demand use of selective serotonin re-uptake inhibitors (SSRIs) and clomipramine, and on-demand topical anaesthetic agents have consistently shown efficacy in PE [783-786]. Long-term outcomes of pharmacological treatments are unknown. An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided, and a treatment algorithm is presented (Figure 7).

Figure 7: Management of premature ejaculation*


Clinical diagnosis of premature ejaculation based on patient +/- partner history
Time to ejaculation (IELT)
Perceived degree of ejaculatory control
Degree of bother/stress
Onset and duration of PE
Psychosocial/relationship issues
Medical history
Physical examination
Treatment of premature ejaculation
Patient counselling/education
Discussion of treatment options
If PE is secondary to ED, treat ED first or concomitantly
Pharmacotherapy (recommended as first-line treatment option in lifelong PE)
Approved on-demand treatment options for PE: Dapoxetine and Lidocaine/prilocaine spray
Off-label treatments include chronic daily use of antidepressants (SSRIs or clomipramine) or tramadol on demand
Combination treatment (pharmacotherapy with behavioural therapy)

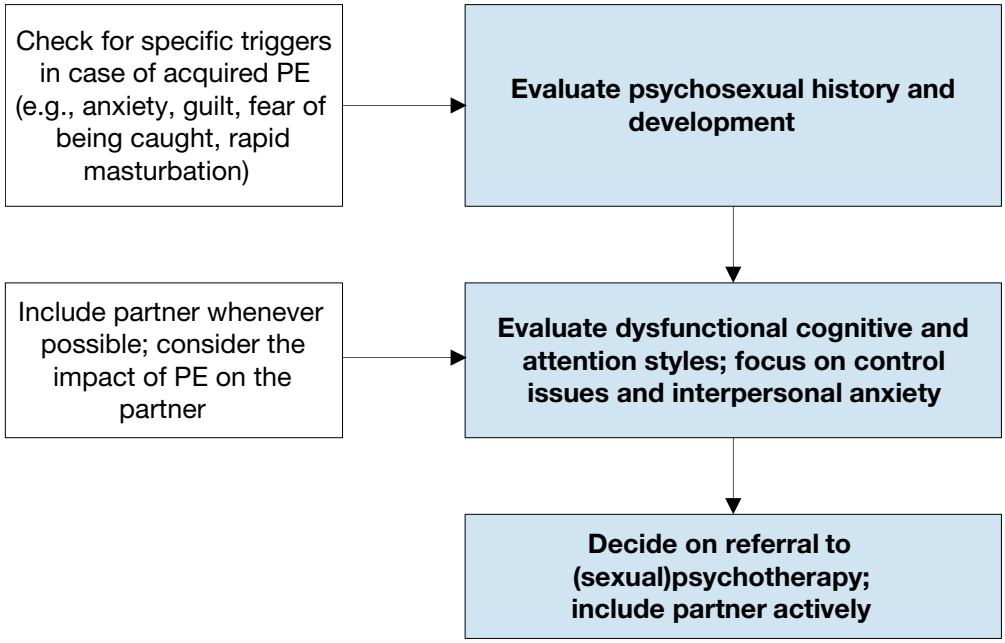
* Adapted from Lue *et al.* 2004 [787].
ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

6.2.6.1 Psychological aspects and intervention

Only a few studies have addressed the psychological factors underpinning PE. Men with PE have been shown to present dysfunctional responsibility attribution patterns regarding their sexual experience. These men blame themselves for their dysfunctional sexual response, even when the negative sexual outcome is unrelated to early ejaculation; additionally, they take less credit for any positive sexual experience they might have [788, 789]. In addition to this style of internalised blame, men with PE focus on bodily sensations and their partners' reactions during sex, to monitor potential signs of threat to their sexual performance. This monitoring process denotes a dysfunctional cognitive and attention style that contributes to the maintenance of PE [461]. Premature ejaculation is further related to increased levels of anxiety, including social anxiety [461, 769]. Yet, it is not known whether anxiety is a precursor or a consequence of PE [699]. Men with PE reported more caution, worry, less motivation toward novelty and exciting situations; that personality style may eventually intersect with PE dynamics [790]. The negative impact of PE on couples has been consistently mentioned. Female partners of men with PE present with an increased likelihood of sexual dysfunction [791, 792]; the intimate sphere, as well as the overall relationship quality, is compromised by PE [780]. An important trigger for seeking help in PE is partner dissatisfaction and the negative impact of PE on the general QoL of the couple [793]. Accordingly, psychosexual interventions, whether these are behavioural, cognitive, or focused on the couple, are aimed at teaching techniques to control/delay ejaculation, gaining confidence in sexual performance, reducing anxiety, and promoting communication and problem solving within the couple [777]. Interventions with a focus on sexual education or acceptance may be positive as well [794]. It is worth noting, however, that psychosexual interventions alone regarding PE lack empirical support. Recent evidence suggests that

start-stop exercises, combined with psycho-education and mindfulness techniques improve PE symptoms, as well as PE-associated distress, anxiety and depression [795]. The potential benefits of mindfulness have been reported [796]. Behavioural therapy may be most effective when used to 'add value' to medical interventions. Combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised trial [778]. Smartphone-delivered psychological intervention, aimed at improving behavioural skills for ejaculatory delay and sexual self-confidence, has positive effects, supporting E-health in the context of PE [797]. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

Figure 8: Key aspects for psychosexual evaluation


Check for specific triggers in case of acquired PE (e.g., anxiety, guilt, fear of being caught, rapid masturbation)
Evaluate psychosexual history and development
Include partner whenever possible; consider the impact of PE on the partner
Evaluate dysfunctional cognitive and attention styles; focus on control issues and interpersonal anxiety
Decide on referral to (sexual)psychotherapy; include partner actively

6.2.6.1.1 Recommendation for the assessment and treatment (psychosexual approach) of PE

Recommendations for assessment	**Strength rating**
Consider sexual history and psychosexual development.	Strong
Consider anxiety, interpersonal anxiety; focus on control issues.	Strong
Include partner if available; check for the impact of PE on the partner.	Strong
Recommendation for treatment (psychosexual approach)	
Use behavioural, cognitive and/or couple therapy approaches. Consider mindfulness exercises.	Weak

6.2.6.2 Pharmacotherapy

6.2.6.2.1 Dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI, with a pharmacokinetic profile suitable for on-demand treatment for PE [775]. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [798, 799]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA. Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with a baseline average IELT < 30 seconds [781, 800, 801].

In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective at improving IELT and increasing ejaculatory control, decreasing distress, and increasing satisfaction [800]. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [781, 802, 803]. Treatment-related adverse effects were dose-dependent and included nausea, diarrhoea, thirst, headache and dizziness [804]. Treatment-emergent adverse events (TEAEs) were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [193]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [800, 805]. Dapoxetine is safer compared with formal anti-depressant compounds that are used for treatment of PE [806].

A low rate (0.1%) of vasovagal syncope was reported in phase 3 studies [807]. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine and dose-titration must be considered [808]. The EMA assessment report for dapoxetine concluded that the potentially increased risk for syncope has been proven manageable with adequate risk minimisation measures [809]. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [810].

Many patients and physicians may prefer using dapoxetine in combination with a PDE5I to extend the time until ejaculation and minimise the risk of ED due to dapoxetine treatment. Phase 1 studies of dapoxetine have confirmed that it does not have any pharmacokinetic interactions with PDE5Is (i.e., tadalafil 20 mg and sildenafil 100 mg) [811]. When dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [812]. A recent RCT including PE patients without ED, demonstrated that combination of dapoxetine with sildenafil can significantly improve IELT values and PROs compared with dapoxetine alone or sildenafil alone, with tolerable adverse events [813]. Efficacy and safety of dapoxetine/sildenafil combination tablets for the treatment of PE have also been reported [814].

Although dapoxetine is the only EMA approved oral drug for treatment of PE, discontinuation rates seem moderate-to-high. The cumulative discontinuation rates increase over time, reaching 90% at 2 years after initiation of therapy. The reasons for the high discontinuation rate are cost (29.9%), disappointment that PE was not curable and the on-demand nature of the drug (25%), adverse effects (11.6%), perceived poor efficacy (9.8%), a search for other treatment options (5.5%), and unknown (18.3%) [815]. Similarly, it was confirmed that a considerable number of patients who were on dapoxetine treatment spontaneously discontinue treatment, while this rate was reported 50% for other SSRIs and 28.8% for paroxetine [816]. In a Chinese cohort study, 13.6% of the patients discontinued dapoxetine due to lack of efficacy (62%), adverse effects (24%), and low frequency of sexual intercourse (14%) [817].

6.2.6.2.2 Off-label use of antidepressants: selective serotonin reuptake inhibitors and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [818, 819] under excitatory or inhibitory influences from the brain and the periphery [739]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT1B and 5-HT2C receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT1A receptors precipitates ejaculation [820].

Selective serotonin re-uptake inhibitors are used to treat mood disorders but can delay ejaculation and therefore have been widely used 'off-label' for PE since the 1990s [821]. For depression, SSRIs must be given for 1-2 weeks to be effective for PE [820]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT1A and 5-HT1B receptors [822]. Commonly used SSRIs include continuous intake of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar efficacy, whereas paroxetine exerts the strongest ejaculation delay [765, 823, 824]. A novel 5-HT1A receptor antagonist, GSK958108, significantly delayed ejaculation in a double-blind, placebo-controlled trial, recently [825].

Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1977 as an effective PE treatment [826, 827]. In a recent RCT, on-demand use of clomipramine 15 mg, 2-6 hours before sexual intercourse was found to be associated with IELT fold change and significant improvements in PRO measures in the treatment group as compared to the placebo group (4.66 ± 5.64 vs. 2.80 ± 2.19, $P < 0.05$). [828, 829]. The most commonly reported TEAEs were nausea in 15.7% and dizziness in 4.9% of men, respectively [828, 829].

Several systematic reviews and meta-analyses of drug treatment have reported that, despite methodological problems in most studies, there remain several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE [765, 783-786]. Based on these meta-analyses, SSRIs may increase the geometric mean IELT by 2.6-13.2-fold. Paroxetine is superior to fluoxetine, clomipramine and sertraline. Sertraline is superior to fluoxetine, whereas the efficacy of clomipramine is not significantly different from that of fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg. There was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective [830, 831].

Ejaculation delay may start a few days after drug intake, but it is more evident after 1-2 weeks as receptor desensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after 6-12 months [826]. Common TEAEs of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration;

TEAEs are usually mild and gradually improve after 2-3 weeks of treatment [800, 826]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of the risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents aged ≤ 18 years with PE, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily-dosed SSRIs, which may be associated with a SSRI withdrawal syndrome [193]. Moreover, PE patients who are trying to conceive should avoid using these medications because of their detrimental effects on sperm cells [832-835].

6.2.6.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [836]. Several trials [706, 837, 838] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. Meta-analyses have confirmed the efficacy and safety of these agents for the treatment of PE [839, 840]. In a recent meta-analysis, the efficacy of local anaesthetics was best among the other treatment options including SSRIs, dapoxetine 30 and 60 mg, PDE5Is and tramadol for < 8 weeks of therapy [841].

6.2.6.2.3.1 Lidocaine/prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine/prilocaine cream increased IELT from one minute in the placebo group to 6.7 minutes in the treatment group [842]. In another randomised, double blind, placebo-controlled trial, lidocaine/prilocaine cream significantly increased the stopwatch-measured IELT from 1.49-8.45 minutes, while no difference was recorded in the placebo group (1.67-1.95 minutes) [843]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. These anaesthetic creams/gels may be transferred to the partner and result in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream to their penis. Alternatively, the penis can be washed to clean off any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples seeking parenthood should not use topical lidocaine/prilocaine-containing substances [844].

6.2.6.2.3.2 Lidocaine/prilocaine spray

The eutectic lidocaine/prilocaine spray is a metered-dose aerosol spray containing purely base forms of lidocaine (150 mg/mL) and prilocaine (50 mg/mL), which has been officially approved by the EMA for the treatment of lifelong PE [845]. Compared to topical creams, the metered-dose spray delivery system has been proved to deposit the drug in a dose-controlled, concentrated film covering the glans penis, maximising neural blockage and minimising the onset of numbness [846], without absorption through the penile shaft skin [847].

To date, one phase 2 proof-of-concept [847] and two phase 3 RCTs [848, 849] have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and the Index of Ejaculatory Control of patients with primary PE, along with an improvement in scores assessing treatment satisfaction (IPE) [848, 849]. Based on these data, according to the patient information leaflet [850], the recommended dose of lidocaine/prilocaine spray is one dose (namely three sprays) to be applied on the glans penis at least 5 minutes before sexual intercourse [851]. Published data showed that lidocaine/prilocaine spray increases IELT over time up to 6.3-fold over 3 months, with a month-by-month improvement through the course of the treatment in long-term studies [852]. A low incidence of local TEAEs in both patients and partners has been reported, including genital hypoaesthesia (4.5% and 1.0% in men and females partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [850, 853].

Lidocaine-only sprays are also effective in the treatment of PE. In a recent RCT, PE patients were randomly allocated to receive either dapoxetine 60 mg or topical lidocaine 10% spray. The geometric mean IELTs were significantly better in the lidocaine compared with dapoxetine group (179.43 vs. 63.44, respectively). However, both groups showed significant improvement compared with baseline IELTs value (63.44 and 179.4 vs. 21.87, $P < .05$) [854]. In another RCT lidocaine 5% spray was compared with alcohol spray (placebo) in the treatment of lifelong PE for 8 weeks; the mean values of the AIPE scores, IELT, and sexual intercourse frequency in the lidocaine 5% spray group were significantly increased compared with the placebo group [855].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [856]. This mechanism of action distinguishes tramadol from

other opioids, including morphine. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours.

A large, randomised, double-blind, placebo-controlled, multicentre 12-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [857].

A bioequivalence study has demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < 2 minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. There are four RCTs comparing the efficacy of tramadol to paroxetine in the literature. On demand tramadol treatment yielded significantly higher IELTs compared to on demand paroxetine treatment arm in three of RCTs [858-860], whilst in the remaining RCT, daily paroxetine was found more effective to treat lifelong PE when compared with on-demand tramadol treatment [861]. A recent meta-analysis including these four RCTs and one single blind study implied that 50 mg tramadol had a significant improvement in the IELT compared with 20 mg paroxetine [862]. Adverse effects were reported at doses used for analgesic purposes (≤ 400 mg daily) and included constipation, sedation and dry mouth. In May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [863]. The tolerability during the 12-week study period in men with PE was acceptable [859]. Several other studies have also reported that tramadol exhibits a significant dose-related efficacy along with potential adverse effects during treatment of PE [864]. The efficacy and safety of tramadol have been confirmed in systematic reviews and meta-analyses [859, 862, 865-868]. The Guidelines Panel considers tramadol as a potential alternative treatment to established first-line therapeutic options in men with PE; however, it should clearly outlined that the use of tramadol has to be considered with caution since there is a lack of data on long-term safety of the compound in this setting.

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

One well-designed, randomised, double-blind, placebo-controlled study compared sildenafil to placebo in men with PE [869]. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and the refractory time to achieve a second erection after ejaculation. Another RCT demonstrated that once-daily 5 mg tadalafil for 6 weeks was effective in improving PROs and was well tolerated by patients with PE [870]. Several open-label studies have shown that combination of PDE5Is and SSRIs is superior to SSRI monotherapy, which has also been recently confirmed by a Bayesian network meta-analysis [841]:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction vs. paroxetine alone [871];
- Sildenafil combined with sertraline improved IELT and satisfaction significantly vs. sertraline alone [872];
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [873];
- Sildenafil combined with dapoxetine (30 mg) improved IELT, satisfaction scores and PEDT vs. dapoxetine, paroxetine or sildenafil monotherapy [813];
- Tadalafil combined with paroxetine significantly improved IELT and satisfaction vs. paroxetine and tadalafil alone [874];
- Sildenafil combined with behavioural therapy significantly improved IELT and satisfaction vs. behavioural therapy alone [875].

Overall, there are limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [876, 877]. In a recent meta-analysis, PDE5Is were found to be significantly more effective than placebo in the treatment of patients with PE and without ED [878]. Some meta-analyses have demonstrated that the combined use of SSRIs and PDE5Is may be more effective than SSRI or PDE5I monotherapy [785, 879-883]. In a recent Bayesian meta-analysis, combined therapy of SSRI and PDE5I was found to be superior to other treatment modalities (including topical creams, tramadol, paroxetine or fluoxetine monotherapy, PDE5I monotherapy, dapoxetine 30 and 60 mg, clomipramine, citalopram, and placebo) lasting > 8 weeks [841].

6.2.6.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research into other treatment options. Considering the abundant α1a-adrenergic receptors in seminal vesicles and the prostate, and the role of the sympathetic system in ejaculation physiology, the efficacy of selective α-blockers in the treatment of PE has been assessed [884-886]. A recent study demonstrated that wake-promoting agent modafinil may be effective in delaying ejaculation and improving PROMs [887]. The efficacy of acupuncture was compared to dapoxetine for the treatment of PE and although acupuncture showed a significant ejaculation-delaying effect, this was less effective as compared with that of dapoxetine [888].

Decreasing penile sensitivity with glans penis augmentation using hyaluronic acid for the treatment of PE was initially proposed by Korean researchers in 2004 [889], and since then has gained popularity mainly in Asian countries [890, 891]. In a randomised controlled cross-over study, hyaluronic acid glans injections were safe with a modest but significant increase in IELT [892]. However, these procedures may result in serious complications and more safety studies must be conducted before recommending this treatment to PE patients [893].

Considering the importance of central oxytocin receptors in ejaculation reflex, several researchers have assessed the efficacy and safety of oxytocin receptor antagonists in the treatment of PE [894]. Epelsiban [895] and cligosiban [896-898] have been found to be safe and mildly effective in delaying ejaculation, but further controlled trials are needed [898].

Retarded ejaculation was associated with the use of pregabalin, a new generation of gapapentinoid, as a side-effect. In a double-blind, placebo-controlled randomised trial where the efficacy and tolerability of on-demand oral pregabalin (150 mg and 75 mg) in treatment of PE was trialled, it was found that IELTs of patients who received 150 mg pregabalin improved significantly (2.45 ± 1.43-fold) compared to those who received 75 mg pregabalin and placebo. Treatment-emergent side effects (blurred vision, dizziness, vomiting) were minimal and did not lead to drug discontinuation.

The role of other proposed treatment modalities for the treatment of PE such as penis-root masturbation [899], vibrator-assisted start-stop exercises [795], transcutaneous functional electric stimulation [900], transcutaneous posterior tibial nerve stimulation [901], and practicing yoga [902] need more evidence to be considered in the clinical setting.

*6.2.7 **Summary of evidence on the epidemiology/aetiology/pathophysiology of PE***

Summary of evidence	LE
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and eutectic lidocaine/prilocaine spray (a topical desensitising agent) which are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a

*6.2.8 **Recommendations for the treatment of PE***

Recommendations	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use off-label tramadol with caution as a viable on-demand alternative to on-demand SSRIs.	Strong
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

6.3 Delayed Ejaculation

*6.3.1 **Definition and classification***

The American Psychiatric Association defines DE as requiring one of two symptoms as follows: marked delay, infrequency, or absence of ejaculation on 75-100% of occasions, that persists for at least 6 months, and which causes personal distress [216]. However, in a recent study, while ejaculatory latency and control were significant criteria to differentiate men with DE from those without ejaculatory disorders, bother/distress did not emerge as a significant factor [903]. Similar to PE, there are distinctions among lifelong, acquired and situational DE [216]. Although the evidence is limited, the prevalence of lifelong DE and acquired DE is estimated around 1% and 4%, respectively [217].

*6.3.2 **Pathophysiology and risk factors***

The aetiology of DE can be psychological, organic (e.g., incomplete spinal cord lesion or iatrogenic penile nerve damage), or pharmacological (e.g., SSRIs, antihypertensive drugs, or antipsychotics) [904, 905] (Table 20). Other factors that may play a role in the aetiology of DE include tactile sensitivity and tissue atrophy [794].

Although low testosterone level has been considered a risk factor in the past [55, 736], more contemporary studies have not confirmed any association between ejaculation times and serum testosterone levels [906, 907]. Idiosyncratic masturbation and lack of desire for stimuli are also proposed risk factors for DE [211-213].

Table 20: Aetiological causes of delayed ejaculation and anejaculation [908]

Ageing Men	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Mullerian duct cyst Wolfian duct abnormalities Prune Belly Syndrome Imperforate Anus Genetic abnormalities
Anatomic causes	Transurethral resection of prostate Bladder neck incision Circumcision Ejaculatory duct obstruction (can be congenital or acquired)
Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/Inflammation	Urethritis Genitourinary tuberculosis Schistosomiasis Prostatitis Orchitis
Endocrine	Hypogonadism Hypothyroidism Prolactin disorders
Medication	Antihypertensives; thiazide diuretics Alpha-adrenergic blockers Antipsychotics and antidepressants Alcohol Antiandrogens Ganglion blockers Selective serotonin reuptake Inhibitors
Psychological	Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

*6.3.3 **Investigation and treatment***

Patients should have a full medical and sexual history performed along with a detailed physical examination when evaluating for DE. It is not uncommon for clinicians to feel uncomfortable with the level of sexual information that is warranted in obtaining a full sexual history. Understanding the details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; cultural context and history of the disorder; quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); partner's assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history-taking [909]. Investigation by a sex therapist is often required to help obtain a complete psychological evaluation. It is incumbent on the clinician to diagnose medical pathologies that cause or contribute to DE, such as assessing the hormonal milieu, anatomy, and overall medical condition. Good communication between the sex therapist and medical practitioner is vital to successful diagnosis and treatment of DE.

6.3.3.1 *Psychological aspects and intervention*

There is scarce literature on the psychological aspects relating to DE, as well as on empirical evidence regarding psychological treatment efficacy. Studies on psychological aspects have revealed that men with DE show a strong need to control their sexual experiences. Delayed ejaculation is associated with difficulties surrendering to sexual pleasure during sex - i.e., the sense of letting go [910] - which denotes a psychological underlying mechanism influencing the reaching of orgasm [911]. As for psychological treatments, these may include, but are not limited to: increased genital-specific stimulation; sexual education; role-playing on his own and in front of his partner; retraining masturbatory practices; anxiety reduction on ejaculation and performance; and, re-calibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality) [909]. A basic understanding of the sexual cycle for their respective partners can assist men and women in managing expectations and in evaluating their own sexual practices. Masturbation techniques that are either solo or partnered can be considered practice for the "real performance" which can eventually result in greater psychosexual arousal and orgasm for both parties [213]. Although masturbation with fantasy can be harmful when not associated with appropriate sexual arousal and context, fantasy can be supportive if it allows blockage of critical thoughts that may be preventing orgasm and ejaculation. Techniques geared towards reduction of anxiety are important skills that can help overcome performance anxiety, as this can often interrupt the natural erectile function through orgasmic progression. Referral to a sexual therapist, psychologist or psychiatrist is appropriate and often warranted.

6.3.3.2 *Pharmacotherapy*

Several pharmacological agents, including cabergoline, bupropion, alpha-1-adrenergic agonists (pseudoephedrine, midodrine, imipramine and ephedrine), buspirone, oxytocin, testosterone, bethanechol, yohimbine, amantadine, cyproheptadine and apomorphine have been used to treat DE with varied success [794]. Unfortunately, there is no FDA or EMA approved medications to treat DE, as most of the cited research is based on case-cohort studies that were not randomised, blinded, or placebo-controlled. Many drugs have been used as both primary treatments and/or as antidotes to other medications that can cause DE. A recent survey of sexual health providers demonstrated an overall treatment success of 40% with most providers commonly using cabergoline, bupropion or oxytocin [912]. However, this survey measured the anecdotal results of practitioners and there was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomised, blinded, comparative trials [908]. In addition to pharmacotherapy, penile vibratory stimulation (PVS) is also used as an adjunct therapy for DE [913]. Another study that used combined therapy of midodrine and PVS to increase autonomic stimulation in 158 men with spinal cord injury led to ejaculation in almost 65% of the patients [914].

6.4 Anejaculation

6.4.1 ***Definition and classification***

Anejaculation involves the complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra [915]. True anejaculation is usually associated with a normal orgasmic sensation and is always associated with central or peripheral nervous system dysfunction or with drugs [916].

6.4.2 ***Pathophysiology and risk factors***

Generally, anejaculation shares similar aetiological factors with DE and retrograde ejaculation (Table 20).

6.4.3 ***Investigation and treatment***

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia, is not effective. In all these cases, and in men who have a spinal cord injury, PVS (i.e., application of a vibrator to the penis) is the first-line therapy. In anejaculation, PVS evokes the ejaculation reflex [917], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an in vitro fertilisation program whenever fathering is desired. If PVS has failed, electro-ejaculation can be the therapy of choice [918]. When electro-ejaculation fails or cannot be carried out, other sperm-retrieval techniques may be used [919]. Anejaculation following either retroperitoneal surgery for testicular cancer or total mesorectal excision can be prevented using unilateral lymphadenectomy or autonomic nerve preservation [920], respectively.

6.5 Painful Ejaculation

6.5.1 ***Definition and classification***

Painful ejaculation is a condition in which a patient feels mild discomfort to severe pain during or after ejaculation. The pain can involve the penis, scrotum, and perineum [921].

6.5.2 *Pathophysiology and risk factors*

Many medical conditions can result in painful ejaculations, but it can also be an idiopathic problem. Initial reports demonstrated possible associations of painful ejaculation with calculi in the seminal vesicles [922], sexual neurasthenia [923], sexually transmitted diseases [921, 924], inflammation of the prostate [237, 925], PCa [926, 927], BPH [235], prostate surgery [928, 929], pelvic radiation [930], herniorrhaphy [931] and antidepressants [932-934]. Further case reports have suggested that mercury toxicity or Ciguatera toxin fish poisoning may also result in painful ejaculation [935, 936]. Psychological issues may also be the cause of painful ejaculation, especially if the patient does not experience this problem during masturbation [937].

6.5.3 *Investigation and treatment*

Treatment of painful ejaculation must be tailored according to the underlying cause, if detected. Psychotherapy or relationship counselling, withdrawal of suspected agents (drugs, toxins, or radiation) [932, 933, 938] or the prescription of appropriate medical treatment (antibiotics, α-blockers or anti-inflammatory agents) may ameliorate painful ejaculation. Behavioural therapy, muscle relaxants, antidepressant treatment, anticonvulsant drugs and/or opioids, pelvic floor exercises, may be implemented if no underlying cause can be identified [939, 940].

6.5.3.1 *Surgical intervention*

If medical treatments fail, surgical operations such as TURP, transurethral resection of the ejaculatory duct and neurolysis of the pudendal nerve have been suggested [941, 942]. However, there is no strong supporting evidence that surgical therapy improves painful ejaculation and therefore it must be used with caution.

6.6 Retrograde ejaculation

6.6.1 *Definition and classification*

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation, as a result of semen passing backwards through the bladder neck into the bladder. Patients may experience a normal, or decreased, orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence [921].

6.6.2 *Pathophysiology and risk factors*

The process of ejaculation requires complex co-ordination and interplay between the epididymis, vas deferens, prostate, seminal vesicles, bladder neck and bulbourethral glands [943]. Upon ejaculation, sperm are rapidly conveyed along the vas deferens and into the urethra via the ejaculatory ducts. From there, the semen progresses in an antegrade fashion, in part maintained by coaptation of the bladder neck and rhythmic contractions of the periurethral muscles, co-ordinated by a centrally mediated reflex [943]. Closure of the bladder neck and seminal emission are initiated via the sympathetic nervous system from the lumbar sympathetic ganglia and subsequently hypogastric nerve. Prostatic and seminal vesicle secretion, as well as contraction of the bulbo-cavernosal, ischio-cavernosal and pelvic floor muscles are initiated by the S 2-4 parasympathetic nervous system via the pelvic nerve [943].

Any factor that disrupts this reflex and inhibits contraction of the bladder neck (internal vesical sphincter) may lead to retrograde passage of semen into the bladder. These can be broadly categorised as pharmacological, neurogenic, anatomic and endocrinal causes of retrograde ejaculation (Table 21).

Table 21: Aetiology of retrograde ejaculation [904]

Neurogenic	Spinal cord injury Cauda equina lesions Multiple sclerosis Autonomic neuropathy Retroperitoneal lymphadenectomy Sympathectomy or aortoiliac surgery Prostate, colorectal and anal surgery Parkinson´s disease Diabetes mellitus Psychological/behavioural
Urethral	Ectopic ureterocele Urethral stricture Urethral valves or verumontaneum hyperplasia Congenital dopamine β-hydroxylase deficiency

Pharmacological	Antihypertensives, thiazide diuretics α-1-Adrenoceptor antagonists Antipsychotics and antidepressants
Endocrine	Hypothyroidism Hypogonadism Hyperprolactinaemia
Bladder neck incompetence	Congenital defects/dysfunction of hemitrigone Bladder neck resection (transurethral resection of the prostate) Prostatectomy

*6.6.3 **Disease management***

Medical and surgical strategies exist for the treatment of retrograde ejaculation. In recent years the reliance on medical treatment as first-line management has become common practice.

6.6.3.1 Pharmacological

Sympathomimetics stimulate the release of noradrenaline as well as activating α- and β-adrenergic receptors, resulting in closure of the internal urethral sphincter, restoring the antegrade flow of semen. The most common sympathomimetics are synephrine, pseudoephedrine hydrochloride, ephedrine, phenylpropanolamine and midodrine [944]. Unfortunately, as time progresses their effect diminishes [945]. Many of the studies published about the efficacy of sympathomimetics in the treatment of retrograde ejaculation suffer from small sample size, with some represented by case reports.

A double-blind controlled study randomised patients to one of four α-adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine and pseudoephedrine) with or without histamine. The patients suffered from failure of ejaculation following retroperitoneal lymphadenectomy. They found that 4 days of treatment prior to ejaculation was most effective and that all the adrenergic agonists restored antegrade ejaculation [944]. In a systematic review, the efficacy of this group of medications was found to be 28% [220]. The adverse effects of sympathomimetics include dryness of mucous membranes and hypertension.

The use of antimuscarinics has been described, including brompheniramine maleate and imipramine, as well as in combination with sympathomimetics. The calculated efficacy of antimuscarinics alone or in combination with sympathomimetics is 22% and 39%, respectively [220]. Combination therapy appears to be more effective although statistical analysis is not yet possible due to the small sample sizes.

6.6.3.2 Management of infertility

Infertility has been the major concern of patients with retrograde ejaculation. Beyond the use of standard sperm-retrieval techniques, such as testicular sperm extraction (TESE), three different methods of sperm acquisition have been identified for the management of infertility in patients with retrograde ejaculation. These include; i) centrifugation and resuspension of post-ejaculatory urine specimens; ii) the Hotchkiss (or modified Hotchkiss) technique; and, iii) ejaculation on a full bladder.

1. *Centrifugation and resuspension.* In order to improve the ambient conditions for the sperm, the patient is asked to increase their fluid intake or take sodium bicarbonate to dilute or alkalise the urine, respectively. Afterwards, a post-orgasmic urine sample is collected by introducing a catheter or spontaneous voiding. This sample is then centrifuged and suspended in a medium. The types of suspension fluids are heterogeneous and can include bovine serum albumin, human serum albumin, Earle's/Hank's balanced salt solution and the patient's urine. The resultant modified sperm mixture can then be used in assisted reproductive techniques. A systematic review of studies in couples in which male partner had retrograde ejaculation found a 15% pregnancy rate per cycle (0-100%) [220].
2. *Hotchkiss method.* The Hotchkiss method involves emptying the bladder prior to ejaculation, using a catheter, and then washing out and instilling a small quantity of Lactated Ringers to improve the ambient condition of the bladder. The patient then ejaculates, and semen is retrieved by catheterisation or voiding [946]. Modified Hotchkiss methods involve variance in the instillation medium. Pregnancy rates were 24% per cycle (0-100%) [220].
3. *Ejaculation on a full bladder.* Few papers have described results using this technique [947, 948]. The patient is encouraged to ejaculate on a full bladder and semen is suspended in Baker's Buffer. The pregnancy rate in the two studies, which included only five patients in total, was 60% [220].

6.7 Anorgasmia

*6.7.1 **Definition and classification***

Anorgasmia is the perceived absence of orgasm and can give rise to anejaculation. Regardless of the presence of ejaculation, anorgasmia can be a lifelong (primary) or acquired (secondary) disorder [217].

*6.7.2 **Pathophysiology and risk factors***

Primary anorgasmia is defined as starting from a man's first sexual intercourse and lasts throughout his life, while for secondary anorgasmia patients should have a normal period before the problem starts [949]. Substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear, are considered risk factors for anorgasmia. Only a few studies have described anorgasmia alone and generally it has been considered as a symptom linked to ejaculatory disorders especially with DE, and therefore, they are believed to share the same risk factors. However, psychological factors are considered to be responsible for 90% of anorgasmia problems [950]. Causes of delayed orgasm and anorgasmia are shown in Table 22 [949].

Table 22: Causes of delayed orgasm and anorgasmia [949]

Endocrine	Testosterone deficiency Hypothyroidism
Medications	Antidepressants Antipsychotics Opioids
Psychosexual causes	
Hyperstimulation	
Penile sensation loss	

*6.7.3 **Disease management***

The psychological/behavioural strategies for anorgasmia are similar to those for DE. The patient and his partner should be examined physically and psychosexually in detail, including determining the onset of anorgasmia, medication and disease history, penile sensitivity and psychological issues. Adjunctive laboratory tests can also be used to rule out organic causes, such as testosterone, prolactin and TSH levels. Patients who have loss of penile sensitivity require further investigations [949].

6.7.3.1 Psychological/behavioural strategies

Lifestyle changes can be recommended to affected individuals including: changing masturbation style; taking steps to improve intimacy, and decreasing alcohol consumption. Several psychotherapy techniques or their combinations have been offered, including alterations in arousal methods, reduction of sexual anxiety, role-playing an exaggerated orgasm and increased genital stimulation [911, 951]. However, it is difficult to determine the success rates from the literature.

6.7.3.2 Pharmacotherapy

Several drugs have been reported to reverse anorgasmia, including cyproheptadine, yohimbine, buspirone, amantadine and oxytocin [952-957]. However, these reports are generally from case-cohort studies and drugs have limited efficacy and significant adverse effect profiles. Therefore, current evidence is not strong enough to recommend drugs to treat anorgasmia.

6.7.3.3 Management of infertility

If patients fail the treatment methods mentioned above, penile vibratory stimulation, electro-ejaculation or TESE are the choice of options for sperm retrieval in anorgasmia cases [949].

6.8 Haemospermia

*6.8.1 **Definition and classification***

Haemospermia is defined as the appearance of blood in the ejaculate. Although it is often regarded as a symptom of minor significance, blood in the ejaculate causes anxiety in many men and may be indicative of underlying pathology [240].

*6.8.2 **Pathophysiology and risk factors***

Several causes of haemospermia have been acknowledged and can be classified into the following sub-categories; idiopathic, congenital malformations, inflammatory conditions, obstruction, malignancies, vascular abnormalities, iatrogenic/trauma and systemic causes (Table 23) [958].

Table 23: Pathology associated with haemospermia [958]

Category	Causes
Congenital	Seminal vesicle (SV) or ejaculatory duct cysts
Inflammatory	Urethritis, prostatitis, epididymitis, tuberculosis, CMV, HIV, Schistosomiasis, hydatid, condyloma of urethra and meatus, urinary tract infections
Obstruction	Prostatic, SV and ejaculatory duct calculi, post-inflammatory, seminal vesicle diverticula/cyst, urethral stricture, utricle cyst, BPH
Tumours	Prostate, bladder, SV, urethra, testis, epididymis, melanoma
Vascular	Prostatic varices, prostatic telangiectasia, haemangioma, posterior urethral veins, excessive sex or masturbation
Trauma/iatrogenic	Perineum, testis, instrumentation, post-haemorrhoid injection, prostate biopsy, vaso-venous fistula
Systemic	Hypertension, haemophilia, purpura, scurvy, bleeding disorders, chronic liver disease, renovascular disease, leukaemia, lymphoma, cirrhosis, amyloidosis
Idiopathic	-

The risk of any malignancy in patients presenting with haemospermia is approximately 3.5% (0-13.1%) [959]. In an observational study of 300 consecutive patients over a 30-month period, 81% had no identified cause of haemospermia. In those patients for whom a cause was identified, the diagnosis varied dependent upon the age of presentation. When the patients were divided into those under and those over 40 years of age, UTIs were more common among younger compared to older patients (15% vs. 10.3%). In the older group (> 40 years), stones (2.2% vs. 1.4%) and malignancy (6.2% vs. 1.4%) were more common when compared with the younger cohort. In the > 40 years group, 13 patients had PCa and one had low-grade urethral carcinoma. In the < 40 years group, one patient had testicular cancer [239]. In a recent study in which 342 patients with haemospermia were included, the most relevant aetiology for haemospermia was inflammation/infection (49.4%) while genitourinary cancers (i.e., prostate and testis) only accounted for 3.2% of the cases [960].

*6.8.3 **Investigations***

As with other clinical conditions, a systematic clinical history and assessment to help identify the cause of haemospermia is undertaken. Although the differential diagnosis is extensive, most cases are caused by infections or other inflammatory processes [240].

The basic examination of haemospermia should start with a thorough symptom-specific and systemic clinical history. The first step is to understand if the patient has true haemospermia. Pseudo-haemospermia may occur as a consequence of haematuria or even suction of a partner's blood into the urethra during copulation [921, 961, 962]. A sexual history should be taken to identify those whose haemospermia may be a consequence of a sexually transmitted disease. Recent foreign travel to areas affected by schistosomiasis or tuberculosis should also be considered. The possibility of co-existing systemic disease such as hypertension, liver disease and coagulopathy should be investigated along with systemic features of malignancy such as weight loss, loss of appetite or bone pain. Examination of the patient should also include measurement of blood pressure, as there have been several case reports suggesting an association between uncontrolled hypertension and haemospermia [963, 964].

Most authors who propose an investigative baseline agree on the initial diagnostic tests, but there is no consensus in this regard [958, 959, 961]. Urinalysis should be performed along with sending the urine for culture and sensitivity testing, as well as microscopy. If tuberculosis or schistosomiasis is the suspected cause, the semen or prostatic secretions should be sent for analysis. A full sexually-transmitted disease screen, including first-void urine as well as serum and genitourinary samples, should be tested for Chlamydia, Ureaplasma and Herpes Simplex virus. Using this strategy, it may be possible to find an infectious agent among cases that would have been labelled as idiopathic haemospermia [965].

Serum PSA should be taken in men aged > 40 years who have been appropriately counselled [241]. Blood work including a full blood count, liver function tests, and a clotting screen should be taken to identify systemic diseases. The question of whether further investigation is warranted depends on clinician judgment, patient age and an assessment of risk factors [958]. Digital rectal examination (DRE) should also be performed and the meatus re-examined after DRE for bloody discharge [966]. Detection of a palpable nodule in the prostate

is important because an association between haemospermia and PCa has been postulated although not completely proven.

Magnetic resonance imaging is being increasingly used as a definitive means to investigate haemospermia. The multiplanar ability of MRI to accurately represent structural changes in the prostate, seminal vesicles, ampulla of vas deferens, and ejaculatory ducts has enabled the technique to be particularly useful in determining the origin of midline or paramedian prostatic cysts and in determining optimal surgical management [967]. The addition of an endorectal coil can improve the diagnostic accuracy for identifying the site and possible causes of haemorrhage [968].

Cystoscopy has been included in most suggested investigative protocols in patients with high-risk features (patients who are refractory to conservative treatment and who have persistent haemospermia). It can provide invaluable information as it allows direct visualisation of the main structures in the urinary tract that can be attributed to causes of haemospermia, such as: polyps, urethritis, prostatic cysts, foreign bodies, calcifications and vascular abnormalities [969, 970].

With the advancement of optics, the ability to create ureteroscopes of diameters small enough to allow insertion into the ejaculatory duct and seminal vesicles has been made possible [971]. In a prospective study, 106 patients with prolonged haemospermia underwent transrectal US and seminal vesiculoscopy. With both methods combined, diagnosis was made in 87.7% of patients. When compared head-to-head, the diagnostic yield for TRUS vs. seminal vesiculoscopy was 45.3% and 74.5%, respectively ($P < 0.001$) [972].

Melanospermia is a consequence of malignant melanoma involving the genitourinary tract and is a rare condition that has been described in two case reports [973, 974]. Chromatography of the semen sample can be used to distinguish the two by identifying the presence of melanin if needed.

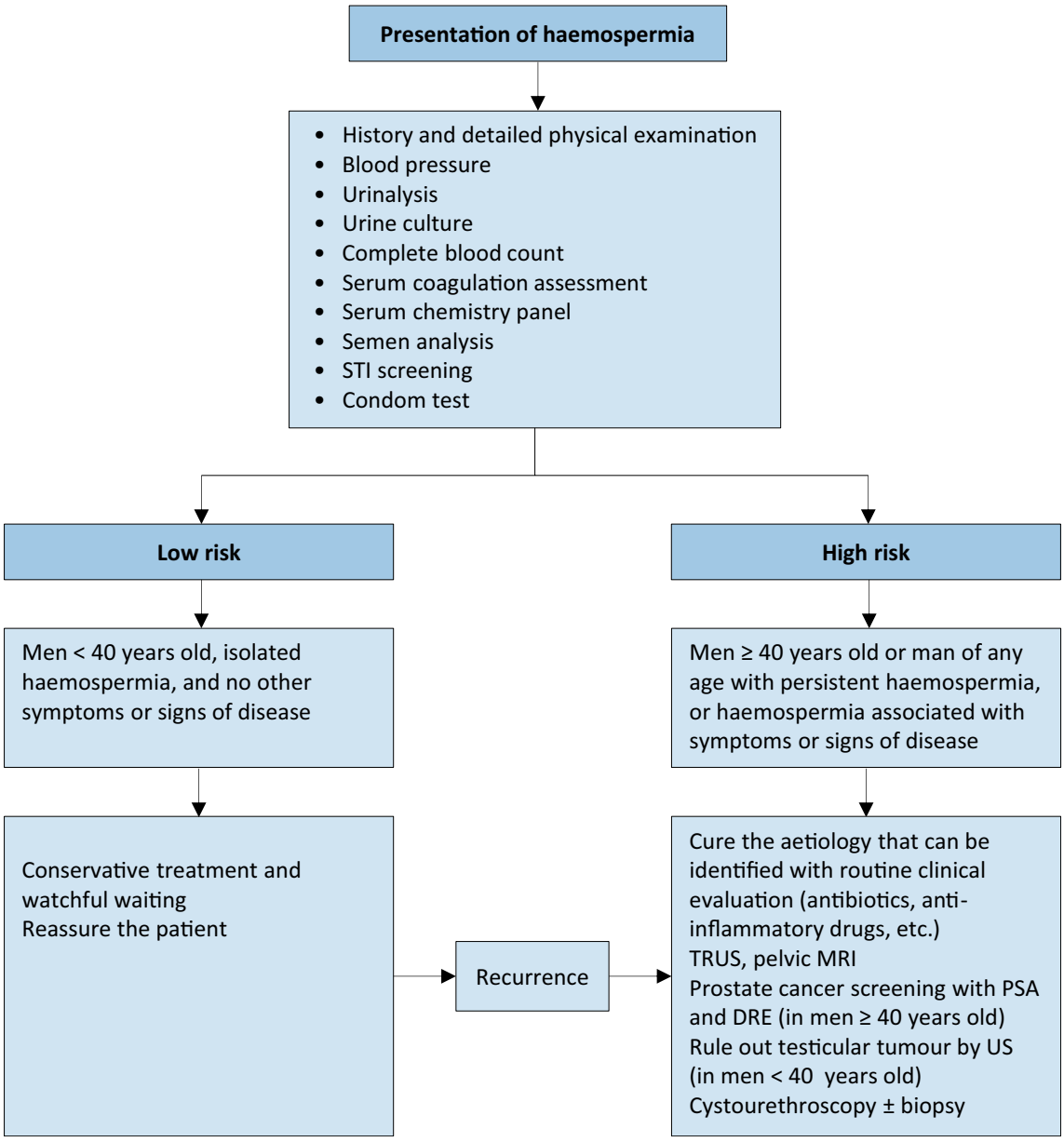
6.8.4 ***Disease management***

Conservative management is generally the primary treatment option when the patients are aged < 40 years and have a single episode of haemospermia. The primary goal of treatment is to exclude malignant conditions like prostate and bladder cancer and treat any other underlying cause. If no pathology is found, then the patient can be reassured [240, 958].

Patients with recurrent haemospermia who are middle-aged, warrant more aggressive intervention. Appropriate antibiotic therapy should be given to patients who have urogenital infections or STIs. Urethral or prostate varices or angiodyplastic vessels can be fulgurated, whereas cysts, either of the seminal vesicles or prostatic urethra, can be aspirated transrectally [240]. Ejaculatory duct obstruction is managed by transurethral incision at the duct opening [975, 976]. Systemic conditions should be treated appropriately [959, 962, 977, 978].

Defining a management algorithm for haemospermia is based on the patient age and degree of haemospermia. Patients often find blood in the ejaculate alarming, and investigations should be aimed at excluding a serious, despite infrequent, underlying cause (e.g., cancer), while at the same time preventing over-investigation and alleviating patient anxiety. The literature describes a multitude of causes for haemospermia, although many of these are not commonly found after investigation. However, men may be stratified into higher-risk groups according to several factors including: age > 40 years, recurrent or persistent haemospermia, actual risk for PCa (e.g., positive family history), and concurrent haematuria. Based upon the literature, a management algorithm is proposed (Figure 9) [959, 962, 977, 978].

Figure 9: Management algorithm for haemospermia [959, 962, 977, 978]


Presentation of haemospermia
History and detailed physical examination
Blood pressure
Urinalysis
Urine culture
Complete blood count
Serum coagulation assessment
Serum chemistry panel
Semen analysis
STI screening
Condom test
Low risk
High risk
Men < 40 years old, isolated haemospermia, and no other symptoms or signs of disease
Men ≥ 40 years old or man of any age with persistent haemospermia, or haemospermia associated with symptoms or signs of disease
Conservative treatment and watchful waiting
Reassure the patient
Recurrence
Cure the aetiology that can be identified with routine clinical evaluation (antibiotics, anti-inflammatory drugs, etc.)
TRUS, pelvic MRI
Prostate cancer screening with PSA and DRE (in men ≥ 40 years old)
Rule out testicular tumour by US (in men < 40 years old)
Cystourethroscopy ± biopsy

STI = Sexually transmitted infections; PSA = Prostate specific antigen; DRE = Digital rectal examination; US = Ultrasonography; TRUS = Transrectal ultrasonography; MRI = Magnetic resonance imaging.

6.9 Recommendations for the management of recurrent haemospermia

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Men aged ≥ 40 years with persistent haemospermia should be screened for prostate cancer.	Weak
Consider non-invasive imaging modalities (TRUS and MRI) in men aged ≥ 40 years or men of any age with persistent or refractory haemospermia.	Weak
Consider invasive methods such as cystoscopy and vesiculoscopy when the non-invasive methods are inconclusive.	Weak

7. LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER

7.1 Definition, classification and epidemiology

It has always been a challenge to define sexual desire properly because it has a complicated nature and it can be conceptualised in many different ways. According to the International Classification of Diseases 10th edition (ICD-10), lack or loss of sexual desire should be the principal problem and not other sexual problems accompanying it such as ED [979]. In the DSM-V, male hypoactive sexual desire disorder (HSDD) is defined as "the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity". The judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning, such as age and general and socio-cultural contexts of the individual's life [216]. According to the fourth International Consultation on Sexual Medicine (ICSM), the definition of male HSDD was proposed as a "persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)" [980]. Although the exact prevalence of low sexual desire (LSD) is unknown, a prevalence of 4.7% was reported in a survey of a population-based sample of middle-aged German men (n = 12,646) [981].

7.2 Pathophysiology and risk factors

Several aetiological factors are considered to contribute to the pathophysiology of LSD. Levine proposed three components of sexual desire as drive (biological), motivation (psychological) and wish (cultural) [982]. However, it is believed that both in the surveys and clinical practice those three components are usually found interwoven [983].

*7.2.1 **Psychological aspects***

The endorsement of negative thoughts during sexual intercourse (i.e., concerns about erection, lack of erotic thoughts, and restrictive attitudes toward sexuality) predicts LSD in men [984, 985]. Furthermore, feeling shame during sexual intercourse, because of negative sexual thoughts (e.g., concern about achieving erection), characterises men with LSD as opposed to women with the same condition [986]. Psychopathological symptoms steaming from a crisis context negatively impacted male sexual desire [453], as well. In addition, dyadic male sexual desire was best accounted by sexual satisfaction [987]. It is worth noting that, despite LSD being less common in men than in women [980], it is the most frequent complaint in couples' therapy [988]. Therefore, the role of relationship factors must be addressed. In addition, anxiety proneness has been associated with LSD in men and is expected to shift men's attention from erotic cues to worrying thoughts, thereby decreasing sexual desire [989]. Finally, is worth noting that current approaches focus on sexual desire discrepancies between partners; the focus on discrepancies rather than on the partner who presents low desire not only reduces stigma, but also provides new opportunities for the management of desire in the relationship context [990].

*7.2.2 **Biological aspects***

Testosterone seems to be essential for a man's sexual desire; however, sexual desire does not directly relate to the circulating level of testosterone, especially in older men [991]. The biological and psychological components that take place in the pathophysiology of LSD are shown in Table 24 [983, 992]. In addition to these factors, there is some speculation about the role of thyroid and oxytocin hormones [720, 993].

Table 24: Common causes of low sexual desire in men [983, 992]

Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome
Renal failure
Coronary disease and heart failure
Ageing

HIV infection
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

*7.2.3 **Risk factors***

In an international survey aimed at estimating the prevalence and correlates of sexual problems in 13,882 women and 13,618 men from 29 countries (Global Study of Sexual Attitudes and Behaviours), risk factors for male LSD were age 60-69 and 70-80 years, poor overall health, vascular diseases, being a current smoker, belief that ageing reduces sex, divorce in the past 3 years, financial problems in the last 3 years, major depression, being worried about the future of a relationship and less than one sexual relation in a week [209]. In a recent study that determined the factors associated with LSD in a large sample of middle-aged German men, PE, ED, and lower urinary tract symptoms were associated with LSD [981]. In contrast, men having more than two children, higher frequency of solo-masturbation, perceived importance of sexuality, and higher sexual self-esteem were less likely to have LSD [981].

7.3 Diagnostic work-up

*7.3.1 **Assessment questionnaires***

Sexual Desire Inventory (SDI) evaluates different components influencing the development and expression of sexual desire [994]. This self-administered questionnaire consists of 14 questions that weigh the strength, frequency, and significance of an individual's desire for sexual activity with others and by themselves. The SDI suggests that desire can be split into two categories: dyadic and solitary desire. While dyadic desire refers to "interest in or a wish to engage in sexual activity with another person and desire for sharing and intimacy with another", solitary desire refers to "an interest in engaging in sexual behaviour by oneself, and may involve a wish to refrain from intimacy and sharing with others" [994].

Physical examination and investigations

Similar to other forms of sexual dysfunctions, a thorough medical and sexual history must be obtained from men who complain of LSD. The depressive symptoms of the patients must be assessed [995] and relationship problems (e.g., conflict with the sexual partner) must be questioned. In the presence of accompanying symptoms suggestive of endocrinological problems, circulating total testosterone [996], prolactin [997] and thyroid hormones [720] levels can be evaluated.

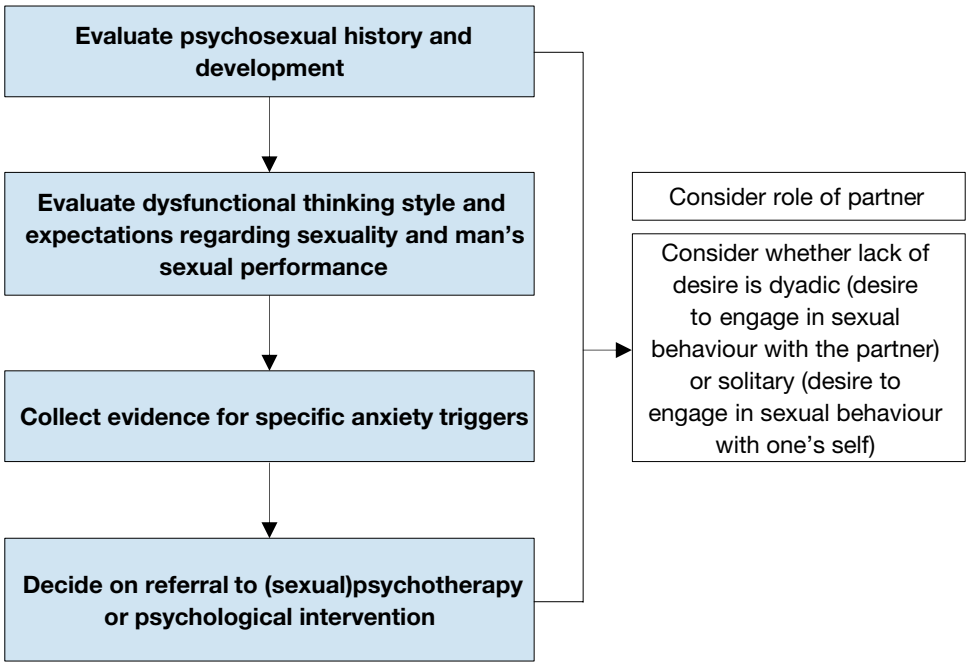
7.4 Disease management

Treatment of LSD should be tailored according to the underlying aetiology.

*7.4.1 **Psychological intervention***

Data on efficacy of psychological interventions for LSD are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for LSD in men [460, 998] (Figure 10). Mindfulness treatments may be a strong candidate, as well [998]. Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the ageing couple (including LSD) as a whole rather than treating the individual patient [999]. Indeed, psychologists are putting more emphasis on the concept of sexual desire discrepancy. Sexual desire discrepancy is often found in couples or partners, and mirror a natural part of life and partners' dynamics. Clinical approaches based on this lens are less stigmatising as they consider the normal variations in sexual desire that occur throughout the lifespan. This intervention option targets couples distressed by sexual desire discrepancies rather than a single individual targeted as the one presenting low sexual desire [990].

Figure 10: Flow-diagram of psychological evaluation of patients with low sexual desire


Evaluate psychosexual history and development
Evaluate dysfunctional thinking style and expectations regarding sexuality and man's sexual performance
Collect evidence for specific anxiety triggers
Decide on referral to (sexual)psychotherapy or psychological intervention
Consider role of partner
Consider whether lack of desire is dyadic (desire to engage in sexual behaviour with the partner) or solitary (desire to engage in sexual behaviour with one's self)

*7.4.2 **Pharmacotherapy***

Low sexual desire secondary to low testosterone levels can be treated with different formulations of testosterone. The favourable effect of testosterone therapy on sexual motivation and the presence of sexual thoughts was shown in a meta-analysis [996]. The aim of treatment should be to reach the physiological range of testosterone (see Section 3.5).

Hyperprolactinaemia can also cause LSD and one of the most relevant aetiological factors is prolactin-secreting pituitary adenomas. These adenomas can be easily diagnosed with MRI of the pituitary gland and can be treated with dopamine agonist agents [1000]. The other accompanying endocrine disorders, such as hypothyroidism, hyperthyroidism and diabetes, should be treated accordingly.

Pharmacotherapy can also be used to treat major depression; however, it should be remembered that antidepressants may negatively affect sexual functioning; therefore, antidepressant compounds with less effect on sexual function should be chosen. Psychotherapy can increase the efficacy of pharmacotherapy, especially for patients whose LSD is due to depression [1001].

7.5 Recommendations for the treatment of low sexual desire

Recommendations	Strength rating
Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires.	Weak
Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction.	Weak
Perform laboratory tests to rule out endocrine disorders.	Strong
Modulate chronic therapies which can negatively impact toward sexual desire.	Weak
Provide testosterone therapy if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

8. PENILE CURVATURE

8.1 Congenital penile curvature

8.1.1 Epidemiology/aetiology/pathophysiology

Congenital penile curvature (CPC) is a rare condition, with a reported incidence of < 1% [1002], although some studies have reported higher prevalence rates of 4-10%, in the absence of hypospadias [1003]. Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In most cases, the curvature is ventral, but it can also be lateral and, more rarely, dorsal [1004].

Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish a diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and more severe curvatures can make intercourse difficult or impossible. Physical examination during erection (alternatively photographic or preferably after intracavernous injection [ICI] of vasoactive drugs) is important to document the curvature and exclude other pathologies [1004].

8.1.2 Disease management

The definitive treatment for this disorder remains surgical and can be deferred until after puberty, although a survey has suggested that men with probable untreated ventral penile curvature report more dissatisfaction with penile appearance, increased difficulty with intercourse, and psychological problems; therefore, supporting surgical correction of CPC in childhood [1005]. Surgical treatments for CPC generally share the same principles as in Peyronie's disease. Plication techniques (Nesbit, 16-dot, Yachia, Essed-Schröeder, and others) with or without neurovascular bundle elevation (medial/lateral) and with or without complete penile degloving, have been described [1006-1015]. Other approaches are based on corporal body de-rotation proposed by Shaeer with different technical refinements that enable correction of a ventral curvature, with reported minimal narrowing and shortening [1016-1019]. There are no direct comparative studies therefore no single technique can be advocated as superior in terms of surgical correction.

8.1.3 Summary of evidence for congenital penile curvature

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a diagnosis of CPC. Physical examination after intracavernosal injection or a photograph during erection is mandatory for documentation of the curvature and exclusion of other pathologies.	3
There is no role for medical management of CPC. Surgery is the only treatment option, which can be deferred until after puberty and can be performed at any time in adult life in individuals with significant functional impairment during intercourse.	3

8.1.4 Recommendation for the treatment congenital penile curvature

Recommendation	Strength rating
Use plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction, although there is currently no optimum surgical technique.	Strong

8.2 Peyronie's Disease

8.2.1 Epidemiology/aetiology/pathophysiology

8.2.1.1 Epidemiology

Epidemiological data on Peyronie's disease (PD) are limited. Prevalence rates of 0.4-20.3% have been published, with a higher prevalence in patients with ED and diabetes [1020-1030]. [1020-1028]. A recent survey has indicated that the prevalence of definitive and probable cases of PD in the USA is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed condition [1031]. Peyronie's disease often occurs in older men with a typical age of onset of 50-60 years. However, PD also occurs in younger men (< 40 years), but at a lesser prevalence than in older men (1.5-16.9%) [1024, 1032, 1033].

8.2.1.2 Aetiology

The aetiology of PD is unknown. However, repetitive microvascular injury or trauma to the tunica albuginea is still the most widely accepted hypothesis to explain the aetiology [1034]. Abnormal wound healing leads to

the remodelling of connective tissue into a fibrotic plaque [1034-1036]. Penile plaque formation can result in a curvature, which, if severe, may impair penetrative sexual intercourse. The genetic underpinnings of fibrotic diatheses, including PD and Dupuytren's disease, are beginning to be understood, although much of the data are contradictory and we do not yet have the basis for predicting who will develop the disease or disease severity (Table 25) [1037, 1038].

Table 25: Genes with involvement in Peyronie's and Dupuytren's diseases (adapted from Herati *et al.* [1037])

Gene	Gene Symbol	Chromosomal Location	Gene Function
Matrix metalloproteinase 2	MMP 2	16q12.2	Breakdown of extracellular matrix
Matrix metalloproteinase 9	MMP 9	20q13.12	Breakdown of extracellular matrix
Thymosin beta-10	TMSB-10	2p11.2	Prevents spontaneous globular actin monomer polymerisation
Thymosin beta-4	TMSB-4	Xq21.3-q22	Actin sequestering protein
Cortactin; amplaxin	CTTN	11q13	Organises cytoskeleton and cell adhesion structures
Transforming protein RhoA H12	RHOA	3p21.3	Regulates cytoskeletal dynamics
RhoGDP dissociation inhibitor	ARHGDIA	17q25.3	Regulates Rho GTPase signaling
Pleiotrophin precursors; osteoblast specific factor 1	PTN/OSF-1	7q33	Stimulates mitogenic growth of fibroblasts and osteoblasts
Amyloid A4 protein precursor; nexin II	PN-II	21q21.3	Cell surface receptor
Defender against cell death 1	DAD1	14q11.2	Prevents apoptosis
Heat Shock 27-kDa protein (HSP27)	HSP27	7q11.23	Actin organisation and translocation from cytoplasm to nucleus upon
Macrophage-specific stimulating factor	MCSF/CSF1	1p13.3	Controls the production, differentiation and function of macrophages
Transcription factor AP-1	AP1	1p32-p31	Key mediator of macrophage education and point of recruitment for immunosuppressive regulatory T cells
Human Early growth response protein 1	hEGR1	5q31.1	Promotes mitosis
Monocyte chemotactic protein 1	MCP1	17q11.2-q12	Chemotactic cytokine for monocytes and basophils
Bone Proteoglycan II precusor; Decorin	DCN	12q21.33	Matrix proteoglycan
T-Cell specific rantes protein precursor	RANTES	17q12	Chemoattractant for monocytes, memory T cells and eosinophils
Integrin Beta-1	ITGB1	10p11.2	Membrane receptor involved in cell adhesion and recognition in a variety of processes including immune response, tissue repair and haemostasis
Osteonectin	SPARC	5q31.3-q32	Matrix protein that facilitates collagen ossification
Ubiquitin	RBX1	6q25.2-q27	Targets substrate proteins for proteasomal degradation
Transcription factor ATF-4	ATF4	22q13.1	Transcriptional regulation of osteoblasts and down-regulates apelin to promote apoptosis
Elastase IIB	ELA2B	1p36.21	Serine protease that hydrolyses matrix protein

c-myc	MYC	8q24.21	Transcription factor that regulates cell cycle progression, apoptosis, and cellular transformations
60 S ribosomal protein L13A	RPL13A	19q13.3	Repression of inflammatory genes
Prothymosin alpha	PTMA	2q37.1	Influences chromatin remodeling, anti-apoptotic factor
Fibroblast tropomyosin	TPM1	15q22.1	Actin-binding protein involved in contractile system of striated and smooth muscle
Myosin light chain	MYL2	12q24.11	Regulatory light chain associated with myosin Beta heavy chain
Filamin	FLN	Xq28	Actin-binding protein that crosslinks actin filaments and links actin to membrane glycoproteins. Interacts with integrins
Calcineurin A subunit alpha	PPP3CA	4q24	Promotes cell migration and invasion and inhibits apoptosis
DNA binding protein inhibitor Id-2	ID2	2p25	Transcriptional regulator that inhibits the function of basic helix-loop-helix transcription factors by preventing their heterodimerisation, negatively regulates cell differentiation
Smooth muscle gamma actin	ACTA2	10q23.3	Plays a role in cell motility, structure and integrity
Desmin	DES	2q35	Forms intra-cytoplasmic filamentous network connecting myofibrils
Cadherin FIB2	PCDHGB4	5q31	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
Cadherin FIB1	DCHS1	11p15.4	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
SMAD family member 7	SMAD7	18q21.1	Interacts with and promotes degradation of TGFBR1
Insulin-like growth factor binding protein 6	IGFBP6	12q13	Negative regulator of cellular senescence inhuman fibroblasts
Collagen 1 alpha	COL1A1	17q21.33	Encodes pro-alpha 1 chains of type 1 collagen
Transforming growth factor, beta 1	TGFB1	19q13.1	Cytokine that regulates proliferation, differentiation, adhesion and cell migration

8.2.1.3 Risk factors

The most commonly reported associated co-morbidity and risk factors are diabetes, hypertension, dyslipidaemias, ischaemic cardiopathy, autoimmune diseases [1039], ED, smoking, excessive alcohol consumption, low testosterone levels and pelvic surgery (e.g., radical prostatectomy) [390, 1024, 1028, 1040-1042]. Dupuytren's contracture is more common in patients with PD affecting 8.3-39% of patients [1025, 1043-1045], while 4-26% of patients with Dupuytren's contracture report PD [1044, 1046, 1047].

8.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [1048]. The first is the active inflammatory phase (acute phase), which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase (chronic phase) with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and of the penile deformity. With time, the penile curvature is expected to worsen in 21-48% of patients or stabilise in 36-67% of patients, while spontaneous improvement has been reported in only 3-13% of patients [1040, 1049-1051]. Overall, penile deformity is the most common first symptom of PD (52-94%). Pain is the second most common presenting symptom of PD, which presents in 20-70% of patients during the early

stages of the disease [1052]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease [1049, 1050]. Palpable plaques have been reported as an initial symptom in 39% of the patients and mostly situated dorsally [50, 1052].

In addition to functional effects on sexual intercourse, men may also suffer from significant psychological distress. Validated mental health questionnaires have shown that 48% of men with PD have moderate or severe depression, sufficient to warrant medical evaluation [1053].

8.2.1.5 Summary of evidence on epidemiology/aetiology/pathophysiology of Peyronie's disease

Summary of evidence	LE
Peyronie's disease (PD) is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which may lead to penile deformity.	2b
The contribution of associated co-morbidity or risk factors (e.g., diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of PD is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the active inflammatory phase (acute phase - painful erections, nodule/plaque), and the second phase is the fibrotic/calcifying phase (chronic or stable phase) with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (21-48%) or stabilisation (36-67%). Pain is usually present during the early stages of the disease, but tends to resolve with time in 90% of men within 12 months of onset.	2a

*8.2.2 **Diagnostic evaluation***

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD. A disease-specific questionnaire (Peyronie's disease questionnaire [PDQ]) has been developed for use in clinical practice and trials. Peyronie's disease questionnaire measures three domains, including psychological and physical symptoms, penile pain and symptom bother [1054].

Clinicians should take a focused history to distinguish between active and stable disease, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have active disease are those with a shorter symptom duration, pain on erection, or a recent change in penile deformity. Resolution of pain and stability of the curvature for at least 3 months are well-accepted criteria of disease stabilisation as well as patients' referral for specific medical therapy [1055, 1056] or surgical intervention, when indicated [1057].

The examination should start with a focused genital assessment that is extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhosen scarring of the plantar fascia [1050]. Penile examination is performed to assess the presence of a palpable nodule or plaque. There is no correlation between plaque size and degree of curvature [1058]. Measurement of the stretched or erect penile length is important because it may have an impact on the subsequent treatment decisions and potential medico-legal implications [1059-1061].

An objective assessment of penile curvature with an erection is mandatory. According to current literature, this can be obtained by several approaches, including home (self) photography of a natural erection (preferably), using a vacuum-assisted erection test or an ICI using vasoactive agents. However, it has been suggested that the ICI method is superior, as it is able to induce an erection similar to or better than that which the patient would experience when sexually aroused [1062-1064]. Computed tomography and MRI have a limited role in the diagnosis of the curvature and are not recommended on a routine basis. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [1065]. Erectile dysfunction is common in patients with PD (30-70.6%) [1066, 1067]. It is mainly an arterial or cavernosal (veno-occlusive) dysfunction in origin [1040, 1058, 1068]. The presence of ED and psychological factors may also have a profound impact on the treatment strategy [1067].

Ultrasound measurement of plaque size is inaccurate but it could be helpful to assess the presence of the plaque and its calcification and location [1069, 1070]. Doppler US may be used for the assessment of penile haemodynamics and ED aetiology [1067].

8.2.2.1 *Summary of evidence for diagnosis of Peyronie's disease*

Summary of evidence	LE
Ultrasound (US) measurement of plaque size is inaccurate and operator dependent.	3
Doppler US may be required to assess penile haemodynamic and vascular anatomy.	2a
Intracavernous injection method is superior to other methods to provide an objective assessment of penile curvature with an erection.	4

8.2.2.2 *Recommendations for diagnosis of Peyronie's disease*

Recommendations	Strength rating
Take a medical and sexual history of patients with Peyronie's disease (PD), include duration of the disease, pain on erection, penile deformity, difficulty in vaginal/anal intromission due to disabling deformity and erectile dysfunction (ED).	Strong
Take a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g., Dupuytren's contracture, Ledderhose disease) in patients with PD.	Strong
Use the intracavernous injection (IC) method in the diagnostic work-up of PD to provide an objective assessment of penile curvature with an erection.	Weak
Use the PD specific questionnaire especially in clinical trials, but mainstream usage in daily clinical practice is not mandatory.	Weak
Do not use ultrasound (US), computed tomography or magnetic resonance imaging to assess plaque size and deformity in everyday clinical practice.	Weak
Use penile Doppler US in the case of diagnostic evaluation of ED, to evaluate penile haemodynamic and vascular anatomy, and to assess location and calcification of plaques, especially prior to surgery.	Weak

8.2.3 ***Disease management***

8.2.3.1 *Conservative treatment*

Conservative treatment of PD is primarily focused on patients in the early stage of the disease as an adjunct treatment to relieve pain and prevent disease progression or if the patient declines other treatment options during the active phase [1050, 1057]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy, shockwave therapy (SWT) and other topical treatments (Table 26).

The results of the studies on conservative treatment for PD are often contradictory, making it difficult to provide recommendations in everyday, real-life settings [1071]. The Panel does not support the use of oral treatments for PD including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium para-aminobenzoate (potaba), omega-3 fatty acids or combination of vitamin E and L-carnitine because of their lack of efficacy (tamoxifen, colchicine, vitamin E and procarbazine) or evidence (potaba, L-carnitine and pentoxyfilline) [1057, 1072-1074]. This statement is based on several methodological flaws in the available studies. These include their uncontrolled nature, the limited number of patients treated, the short-term follow-up and the different outcome measures used [1075, 1076]. Even in the absence of adverse events, treatment with these agents may delay the use of other efficacious treatments.

Table 26: Conservative treatments for PD

Oral treatments
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors (PDE5Is)
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase

Interferon α2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Extracorporeal shockwave treatment
Other
Traction devices
Multimodal treatment

8.2.3.1.1 Oral treatment

Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors were first suggested as a treatment for PD in 2003 to reduce collagen deposition and increase apoptosis through the inhibition of transforming growth factor (TGF)-b1 [1077-1079]. A retrospective study of 65 men suggested the use of PDE5Is as an alternative for the treatment of PD. The results indicated that treatment with tadalafil was helpful in decreasing curvature and remodelling septal scars when compared to controls [1080]. Another recent study concluded that sildenafil was able to improve erectile function and pain in PD patients. Thirty-nine patients with PD were divided into two groups receiving vitamin E (400 IU) or sildenafil 50 mg for 12 weeks and significantly better outcomes in pain and IIEF score were seen in the sildenafil group [1081].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered to patients in active-phase PD in order to manage penile pain, which is usually present in this phase. Pain levels should be periodically reassessed in monitoring treatment efficacy.

8.2.3.1.2 Intralesional treatment

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure, particularly when a dense or calcified plaque is present.

Calcium channel antagonists: verapamil and nicardipine

The rationale for intralesional use of channel antagonists in patients with PD is based on in vitro research [1082, 1083]. Due to the use of different dosing schedules and the contradictory results obtained in published studies, the evidence is not strong enough to support the clinical use of injected channel blockers verapamil and nicardipine and the results do not demonstrate a meaningful improvement in penile curvature compared to placebo [1084-1089]. In fact, most of the studies did not perform direct statistical comparison between groups.

Collagenase of Clostridium histolyticum

Collagenase of *Clostridium histolyticum* (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the PD plaque [1090-1093]. Intralesional injection of CCH has been used in the treatment of PD since 1985. In 2014 the EMA approved CCH for the nonsurgical treatment of the stable phase of PD in men with palpable dorsal plaques in whom abnormal curvature of 30-90° and non-ventrally located plaques are present. It should be administered by a healthcare professional who is experienced and properly trained in the administration of CCH treatment for PD [1094, 1095].

The original treatment protocol in all studies consists of two injections of 0.58 mg of CCH 24-72 hours apart every 6 weeks for up to four cycles. Data from IMPRESS (Investigation for Maximal Peyronie´s Reduction Efficacy and Safety Studies) II and II studies [976], as well as post approval trials [1096], which demonstrated the efficacy and safety of this treatment, are summarised in Table 27.

Table 27: Clinical evidence supporting CCH treatment

Author/year [Ref]	Study type	Special considerations	No. of patients	No. of injections	Decrease in PC in CCH group
Gelbard *et al.* (2013) [1097]	Phase 3 randomised double blinded controlled trial	Pilot study	551	8 (in 78.8% of patients)	34% (17.0 ± 14.8 degrees)
Levine *et al.* (2015) [1098]	Phase 3 Open-label	IMPRESS based	347	≤ 8	34.4% (18.3 ± 14.02 degrees)
Ziegelmann *et al.* (2016) [1099]	Prospective double-blinded trial	IMPRESS based	69	Mean = 6	38% (22.6 ± 16.2 degrees)
Yang and Bennett (2016) [1100]	Prospective study	Included patients in acute phase	37 in SP 12 in AP	Median in SP = 6 Median in AP = 2.5	32.4% (15.4 degrees) AP = 20 degrees
Nguyen *et al.* (2017) [1065]	Retrospective study	Included patients in acute phase	126 in SP 36 in AP	Mean = 3.2	SP = 27.4% (15.2 ± 11.7 degrees) AP = 27.6% (18.5 ± 16.2 degrees) N/S differences in final change in curvature between group 1 (16.7º) and group 2 (15.6º) p = 0.654
Anaissie *et al.* (2017) [1101]	Retrospective study	Included patients in acute phase	77	Mean = 6.6	29.6% (15.3 ± 12.9 degrees)
Abdel Raheem *et al.* (2017) [1102]	Prospective study	Shortened protocol	53	Mean = 3	31.4% (17.6 degrees)
Capece *et al.* (2018) [1103]	Prospective multicentric study	Shortened protocol	135	Mean = 3	42.9% (19.1 degrees)

SP = Stable phase; AP = Acute phase; N/S = Non-significant.

The average improvement in curvature was 34% compared to 18.2% in the placebo group. Three adverse events of corporeal rupture were surgically repaired. The greatest chance of curvature improvement is for curvatures between 30° and 60°, longer duration of disease, IIEF > 17, and no calcification [1056]. An 18.2% improvement from baseline in the placebo arm was also observed. These findings raise questions regarding the alleged role of plaque injection and penile modelling, regardless of the medication, in improving outcomes in men with PD as the placebo or modelling arm resulted in high curvature reduction compared to treatment.

The conclusion of the IMPRESS I and II studies is that that CCH improves PD both physically and psychologically [1097]. A *post hoc* meta-analysis of the IMPRESS studies demonstrated better results in patients with < 60° of curvature, > 2 years evolution, no calcification in the plaque and good erectile function [1096].

Thereafter, a modified short protocol consisting of administration of a single (0.9 mg, one vial) injection per cycle distributed along three lines around the point of maximum curvature up to three cycles, separated by 4-weekly intervals, has been proposed, and replaces the physician modelling with a multi-modal approach through penile stretching, modelling and VED at home [1102]. The results from this modified protocol were comparable to the results of the IMPRESS trials and appeared to decrease the cost and duration of treatment, although these represent non-randomised study protocols. These results were further explored in a prospective non-randomised multi-centre study [982]. In another large single-arm multi-centre clinical study using the shortened protocol, longer PD duration, greater baseline PC and basal and dorsal plaque location were identified as clinically significant predictors of treatment success [1104]. Accordingly, a nomogram developed to predict treatment success after CCH for PD showed that patients with longer PD duration, greater baseline

penile curvature and basal plaque location had a greater chance of treatment success [1104]; however, these findings need to be externally validated.

Regarding safety concerns, most PD patients treated with CCH experienced at least one mild or moderate adverse reaction localised to the penis (penile haematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%)), which resolved spontaneously within 14 days of injection [1105]. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. Serious treatment-emergent adverse events (TEAEs) (0.9%) include penile haematoma and corporeal rupture that require surgical treatment. According to IMPRESS data and the shortened protocol, to prevent serious TEAEs men should be advised to avoid sexual intercourse in the 4 weeks following injection. Recent preliminary data suggest that treatment in the acute phase of the disease can be effective and safe [1065, 1099, 1100, 1106-1108].

In conclusion, CCH is a safe and established treatment for stable-phase disease. More recent evidence suggests that CCH also has a role in affecting the progression of active-phase disease, thus supporting the idea that the indications for CCH use could be expanded, although there is the possibility of a high placebo effect. It should also be noted that there is a large effect of traction or modelling in controlled studies, while studies reporting on modified protocols have small numbers of patients and are largely uncontrolled. Therefore, patients should be counselled fully on the efficacy of collagenase and the high cost of treatment.

It has been suggested that those patients with severe curvature may also benefit from CCH injections because of a potential downgrading of the penile curvature: a decrease in curvature may allow for a penile plication procedure instead of a plaque incision and grafting procedure, therefore avoiding the more negative impact on erectile function. However, further investigation is needed to validate these initial findings [1065, 1100].

The Panel has agreed to keep the whole set of information and recommendations regarding the use of CCH in men with PD despite the recent official withdrawal of the product from the European market by the company.

Interferon α-2b

Interferon α-2b (IFN-α2b) has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production by fibroblasts and improve the wound healing process from PD plaques in vitro [1109]. Intralesional injections (5x10^6 units of IFN-α2b in 10 mL saline every 2 weeks over 12 weeks for a total of six injections) significantly improved penile curvature, plaque size and density, and pain compared to placebo. Additionally, penile blood flow parameters are benefited by IFN-α2b [1095, 1110, 1111]. Regardless of plaque location, IFN-α2b is an effective treatment option. Treatment with IFN-α2b provides a > 20% reduction in curvature in most men with PD, independent of plaque location [1112]. Given the mild adverse effects, which include sinusitis and flu-like symptoms, which can be effectively treated with NSAIDs before IFN-α2b injection, and the moderate strength of data available, IFN-α2b is currently recommended for treatment of stable-phase PD.

Steroids, hyaluronic acid and botulinum toxin (botox)

In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [1113]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [1114]. The effect of hyaluronic acid treatment in patients with PD was investigated in recent studies [1115-1118]. In a non-randomised study, intralesional injection of hyaluronic acid was compared to intralesional verapamil in acute phase PD and significant improvement of pain, curvature and IIEF-15 was observed [1117]. In a RCT, oral administration of hyaluronic acid combined with intralesional injection has been found superior to intralesional injection only and improvement of 7.8±3.9 degrees in curvature and reduction in plaque size of 3.0 mm was observed (LE:1b) [1118]. As only a single study evaluated intralesional botox injections in men with PD, the Panel conclude that there is no robust evidence to support these treatments [1119].

Platelet Rich Plasma (PRP)

In an experimental in-animal study investigating the effect of PRP on PD, no reduction in terms of plaque size has been shown, but the use of PRP resulted in increase in type III/type I collagen ratio and collagen/smooth muscle ratio [1120]. Few studies in humans have evaluated the effect of PRP on penile curvature, plaque size, PDQ and IIEF with low level of evidence (LE:3) (Table 28). Significant improvement has been found in penile curvature, and IIEF in two studies. Another two studies showed additional improvement in plaque size and PDQ. The effect of PRP in patients with Peyronie's disease remains to be proven and should be considered as experimental.

Table 28: Studies on PRP in penile curvature and/or PD patients

Author	No of patients	Age (years)	Number of injections	IIEF score	Curvature	Decrease in plaque size	Pain	PDQ
Virag *et al.* (2014) [1121]	13	57.5	4 (with HA) (2 injections /month)	Improvement in all patients	30%	53%	N/A	N/A
Virag *et al.* (2017) [1122]	90	N/A	4 (2 injections /month)	+4.1	%39.65	-1.11 mm	N/A	improvement
Marcovici *et al.* (2018) [1123]	1	54	2	N/A	20%	N/A	N/A	N/A
Matz *et al.* (2018) [613]	11	46	2.1	+4.14	Subjective improvement	N/A	N/A	N/A
Notsek *et al.* (2019) [1124]	59	N/A	1	improvement	50%	50%	84%	N/A

HA = hyaluronic acid; IIEF = International Index of Erectile Function; N/A = not applicable; PDQ = Peyronie's disease questionnaire.

8.2.3.1.3 Topical treatments

Topical verapamil and H-100 Gel

There is no sufficient and unequivocal evidence that topical treatments (verapamil, H-100 Gel [a compound with nicardipine, superoxide dismutase and emu oil] or steroids) applied to the penile shaft, with or without the use of iontophoresis (now known as transdermal electromotive drug administration), result in adequate levels of the active compound within the tunica albuginea [1125-1128]. Therefore, the Panel does not support the use of topical treatments for PD applied to the penile shaft.

Extracorporeal shockwave treatment

The mechanical shear stress provoked by low-intensity extracorporeal shock wave treatment (LI-ESWT) on the treated tissue was deemed to induce neovascularisation and to enhance local blood flow [1071]. The mechanism of action involved in ESWT for PD is still unclear, but there are two hypotheses: (i) SWT works by directly damaging and remodelling the penile plaque; and (ii) SWT increases the vascularity of the area by generating thermodynamic changes resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [1129, 1130].

Four RCTs and one meta-analysis [1131-1135] assessed the efficacy of ESWT for PD. Three were sham-controlled trials while one compared ESWT with the combination of ESWT and PDE5I (tadalafil) [1129].

All trials showed positive findings in terms of pain relief, but no effect on penile curvature and plaque size. Inclusion criteria varied widely among studies and further investigation is needed. The results are summarised in Table 29.

Table 29: Efficacy of ESWT in the treatment of PD

Author/Year [Ref]	No. of cases/ controls	Inclusion criteria	Comparator	Follow-up	Treatment protocol	Results	Adverse effects
Palmieri *et al.* 2009 [1131]	50 / 50	PD < 12 mo. No previous treatment	Sham therapy	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm^2, 4 Hz	**Change in IIEF** (+5.4points) **Pain reduction** (-5.1 points) **Change in curvature** (-1.4°) **Plaque size** (-0.6 in)	None

Chitale *et al.* 2010 [1132]	16 / 20	Stable PD > 6 mo. No previous treatment	Sham therapy	6 month	1 session/week x 6 weeks. No other parameters mentioned.	**Change in IIEF** Significant in both groups **Pain reduction** Significant in both groups **Change in curvature** N/S **Plaque size** N/S	None
Palmieri *et al.* 2011 [1133]	50 / 50	PD < 12 mo. Painful erections Presence of ED	ESWT + tadalafil 5 mg OD	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm^2, 4 Hz	**Change in IIEF** Significant in both groups **Pain reduction** Significant in both groups **Change in curvature** N/S **Plaque size** N/S	None
Hatzichristodoulou *et al.* 2013 [1134]	51 / 51	Stable PD > 3 mo. Previous unsuccessful oral treatment	Sham therapy	1 month	1 session/week x 6 weeks 2000 sw, 0.29 mJ/mm^2	**Change in IIEF** N/A **Pain reduction** (-2.5 points) **Change in curvature** N/S **Plaque size** N/S	Ecchymosis 4,9%

N/A = no assessed; N/S = no significant; IIEF = International index of erectile function; VAS = Visual Analogic Scale; ED = Erectile dysfunction.

Penile traction therapy

In men with PD, potential mechanisms for disease modification with penile traction therapy (PTT) have been described, including collagen remodelling via decreased myofibroblast activity and matrix metalloproteinase up-regulation [1136, 1137].

The stated clinical goals of PTT are to non-surgically reduce curvature, enhance girth, and recover lost length, which are attractive to patients with PD. However, clinical evidence is limited due to the small number of patients included (267 in total), the heterogeneity in the study designs, and the non-standardised inclusion and exclusion criteria which make it impossible to draw any definitive conclusions about this therapy [1138-1142].

Most of the included patients will need further treatment to ameliorate their curvature for satisfactory sexual intercourse. Moreover, the effect of PTT in patients with calcified plaques, hourglass or hinge deformities which are, theoretically, less likely to respond to PTT has not been systematically studied. In addition, the treatment can result in discomfort and be inconvenient due to use of the device for an extended period (2-8 hours daily), but has been shown to be tolerated by highly-motivated patients. There were no serious adverse effects, including skin changes, ulcerations, hypo-aesthesia or diminished rigidity [1140, 1143].

In conclusion, PTT seems to be effective and safe for patients with PD, but there is still lack of evidence to give any definitive recommendation in terms of monotherapy for PD.

Table 30: Summary of clinical evidence of PTT as monotherapy

Author/year	Study type	Device	No. of patients	Hours of use	Result
Levine *et al.* (2008)	Pilot Prospective, uncontrolled	Fast Size®	10	2-8h 6 months	Mean reduction in PC 33% (51°-34°) SPL: + 0.5-2 cm EG: + 0.5-1 cm IIEF: + 5.3

Gontero *et al.* (2009)	Phase II Prospective Uncontrolled	Andropenis®	15	> 5h 6 months	Mean reduction in PC: N/S SPL: + 0.8 cm (6 mo) + 1.0 cm (12 mo)
Martinez-Salamanca *et al.* (2014)	Prospective, controlled, open label Men in AP	Andropenis®	96 55 (PD) 41 (NIG)	6-9h (4.6 h/d) 6 months	Mean reduction in PC: 20º (33º-15º) p < 0.05. SPL: + 1.5 cm (6 mo) EG: + 0.9 cm (6 mo)
Moncada *el al.* (2018)	Controlled multicenter trial Men in CP	Penimaster®PRO	80 41 (PTT) 39 (NIG)	3-8h 3 months	Mean reduction in PC: 31º (50º-15º). SPL: + 1.8 cm (3 mo) EG: + 0.9 cm (6 mo) IEEF: + 2.5
Ziegelmann *et al.* (2019) [1142]	Randomised, prospective, controlled, single blind study Men in CP and contols 3:1	Restorex®	110	30-90 min/day 3 months	Mean reduction in PC (3 mo): 13.3º (PTT) + 1.3º (control) p < 0.001 SPL: + 1.5 cm (PTT) + 0 cm (control) p < 0.001 IIEF: + 4.3 (PTT) -0.7 (control) p = 0.01

NIG = non-intervention group; IIEF = International Index of Erectile Function; N/S = Not significant; PD = Peyronie´s Disease; AP = Acute phase; CP = Chronic phase; SPL - Stretched penile length; EG = Erect girth.

Vacuum erection device

Vacuum erection device (VED) therapy results in dilation of cavernous sinuses, decreased retrograde venous blood flow and increased arterial inflow [1144]. Intracorporeal molecular markers are affected by VED application, including decreases in hypoxia-inducible factor-1α, TGF-β1, collagenase, and apoptosis, and increases endothelial nitric oxide synthase (eNOS) and α-smooth muscle actin, given their role in the pathogenesis of PD [1145]. Only one clinical study assessed the efficacy of VED therapy in mechanically straightening the penile curvature of PD as monotherapy and further investigation is needed [1146].

8.2.3.1.4 Multimodal treatment

There are some data suggesting that a combination of different oral drugs can be used for treatment of the acute phase of PD. However, there does not seem to be a consensus on which drugs to combine or the optimum drug dosage; nor has there been a comparison of different drug combinations.

A long-term study assessing the role of multimodal medical therapy (injectable verapamil associated with antioxidants and local diclofenac) demonstrated that it is efficacious to treat PD patients. The authors concluded that combination therapy reduced pain more effectively than verapamil alone, making this specific combination treatment more effective compared to monotherapy [1145]. Furthermore, combination protocols including injectable therapies, such as CCH, have been studied in controlled trials. The addition of adjunctive PTT and VED has been described; however, limited data are available regarding its use [1147].

Penile traction therapy has been evaluated as an adjunct therapy to intralesional injections with interferon, verapamil, or CCH [1085, 1148, 1149]. These studies have failed to demonstrate significant improvements in penile length or curvature, with the exception of one subset analysis identifying a 0.4 cm length increase among men using the devices for > 3 hours/day [1149]. A meta-analysis demonstrated that men who used PTT as an adjunct to surgery or injection therapy for PD had, on average, an increase in stretched penile length (SPL) of 1 cm compared to men who did not use adjunctive PTT. There was no significant change in curvature between the two groups [1150].

Data available on the combined treatment of CCH and the use of VED between injection intervals have shown significant mean improvements in curvature (-17°) and penile length (+0.4 cm) after treatment. However, it is not possible to determine the isolated effect of VED because of a lack of control groups [1102, 1150].

Recent data have suggested that combination of PDE5I (sildenafil 25 mg twice daily) after CCH treatment (shortened protocol combined with VED) is superior to CCH alone for improving penile curvature and erectile function. Further studies are necessary to externally validate those findings.

8.2.3.1.5 Summary of evidence for conservative treatment of Peyronie's disease

Summary of evidence	LE
Conservative treatment for PD is primarily aimed at treating patients in the early stage of the disease in order to relieve symptoms and prevent progression.	3c
There is no convincing evidence supporting oral treatment with acetyl esters of carnitine, vitamin E, potassium para-aminobenzoate (potaba) and pentoxifylline.	3c
Due to adverse effects, treatment with oral tamoxifen is no longer recommended.	3c
Nonsteroidal anti-inflammatory drugs can be used to treat pain in the acute phase.	5
Intralesional treatment with calcium channel antagonists: verapamil and nicardipine are no longer recommended due to contradictory results.	1b
Intralesional treatment with Collagenase *clostridium histolyticum* showed significant decreases in penile curvature, plaque diameter and plaque length in men with stable disease.	1b
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	2b
Intralesional treatment with steroids are no longer recommended due to adverse effects, including tissue atrophy, thinning of the skin and immunosuppression.	3c
No robust evidence is available to support treatment with intralesional hyaluronic acid or botulinum toxin.	3c
Intralesional hyaluronic acid may be used to improve pain, penile curvature and IIEF scores.	2b
Combination of oral and intralesional hyaluronic acid treatment improves penile curvature and plaque size.	1b
There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea.	3c
The use of iontophoresis is not recommended due to the absence of efficacy data.	3c
Extracorporeal shockwave treatment may be offered to treat penile pain, but it does not improve penile curvature and plaque size.	2b
Treatment with penile traction therapy alone or in combination with injectable therapy as part of a multimodal approach may reduce penile curvature and increase penile length, although studies have limitations.	3c

8.2.3.1.6 Recommendations for non-operative treatment of Peyronie's disease

Recommendations	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Discuss with patients all the available treatment options and expected results before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifylline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Nonsteroidal anti-inflammatory drugs can be used to treat penile pain in the acute phase of PD.	Strong
Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD.	Weak
Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30° seeking a minimal invasive procedure.	Strong
Intralesional therapy with Collagenase *clostridium histolyticum* may be offered in patients with stable PD and dorsal or lateral curvature > 30°, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong
Do not use intralesional platelet-rich plasma or hyaluronic acid – either alone or in combination with oral treatment – to reduce penile curvature, plaque size or pain outside the confines of a clinical trial.	Weak

Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

8.2.3.2 Surgical treatment

Although conservative treatment for PD may resolve painful erections in most men, only a small percentage experience significant straightening of the penis. The aim of surgery is to correct curvature and allow penetrative intercourse. Surgery is indicated in patients with significant penile deformity and difficulty with intercourse associated with sexual bother. Patients must have a stable disease for 3-6 months (or more than 9-12 months after onset of PD) [1048, 1057, 1151]. In addition to this requirement, there are other situations that may precipitate an indication for surgery, such as failed conservative or medical therapies, extensive penile plaques, or patient preference, when the disease is stable [1152, 1153].

Before considering reconstructive surgery, it is recommended to document the size and location of penile plaques, the degree of curvature, complex deformities (hinge or hourglass), the penile length and the presence or absence of ED. The potential aims and risks of surgery should be fully discussed with the patient so that he can make an informed decision [1151]. Specific issues that should be mentioned during this discussion are: risk of penile shortening; ED, penile numbness; and delayed orgasm, the risk of recurrent curvature, potential for palpation of knots and stitches underneath the skin, potential need for circumcision at the time of surgery, residual curvature and the risk of further penile wasting with shortening procedures [1057, 1154]. Selection of the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [1057]. Patient expectations from surgery must also be included in the pre-operative assessment. The main objective of surgery is to achieve a “functionally straight” penis, and this must be fully understood by the patient to achieve the best possible satisfaction outcomes after surgery [1151, 1155].

Three major types of reconstruction may be considered for PD: (i) tunical shortening procedures; (ii) tunical lengthening procedures; and, (iii) penile prosthesis implantation, with or without adjunct straightening techniques in the presence of concomitant ED and residual curvature [1156, 1157].

Tunical shortening procedures achieve straightening of the penis by shortening the longer, convex side of the penis to make it even with the contralateral side. Tunical lengthening procedures are performed on the concave side of the penis after making an incision or partial excision of the plaque, with coverage of the defect with a graft. Although tunical lengthening procedures rarely lead to long-term penile length gain, they aim to minimise penile shortening caused by plication of the tunica albuginea, and correct complex deformities. In practice, tunical lengthening procedures are often combined with penile plication or shortening procedures to correct residual curvature [1158]. In patients with PD and ED not responding to medical treatments, penile prosthesis implantation can be considered with correction of the curvature including adjunct techniques (modelling, plication or incision/excision with grafting).

Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) should be considered the standard approach for all types of procedures, although modifications have been described. Only one study has suggested that circumcision is not always necessary (e.g., in cases where the foreskin is normal pre-operatively) [1159]. Non-degloving techniques have been described that have been shown to prevent ischaemia and lymphatic complications after subcoronal circumcision [1160, 1161].

There are no standardised questionnaires for the evaluation of surgical outcomes. Data from well-designed prospective studies are scarce, with low levels of evidence. Data are mainly based on retrospective single-centre studies, typically non-comparative and non-randomised, or on expert opinion [1057, 1162]. Therefore, surgical outcomes must be treated with caution.

8.2.3.2.1 Tunical shortening procedures

For men with good erectile function, adequate penile length, without complex deformities, such as an hourglass or hinge type narrowing abnormality, and non-severe curvature, a tunical shortening procedure can be considered an appropriate surgical approach. Numerous different techniques have been described, although they can be classified as excisional, incisional and plication techniques.

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite to the point of maximum curvature with a non-elastic corporal segment to treat CPC [1163]. Thereafter, this technique became a successful treatment option for PD-associated penile curvature [1164]. This operation is based on a 5-10 mm

transverse elliptical excision of the tunica albuginea or ~1 mm for each 10° of curvature. The overall short- and long-term results of the Nesbit operation are excellent [1165-1169]. Some modifications of the Nesbit procedure have been described (partial thickness shaving instead of conventional excision; underlapped U incision) with similar results, although these are in non-randomised studies [1170-1174].

The Yachia technique is based on a completely different concept, as it utilises the Heinke-Mikowitz principle for which a longitudinal tunical incision is closed transversely to shorten the convex side of the penis. This technique, initially described by Lemberger in 1984, was popularised by Yachia in 1990, when he reported a series of 10 cases [1175-1180].

Pure plication techniques are simpler to perform. They are based on single or multiple plications performed without making excisions or incisions, to limit the potential damage to the veno-occlusive mechanism [1059, 1181-1197]. Another modification has been described as the '16-dot' technique that consists of application of two pairs of parallel Essed-Schroeder plications tensioned more or less depending on the degree of curvature [1174, 1198-1200]. The use of non-absorbable sutures or longer-lasting absorbable sutures may reduce recurrence of the curvature (Panel expert opinion). Results and satisfaction rates are both similar to the incision/excision procedures.

In general, using these tunical shortening techniques, complete penile straightening is achieved in > 85% of patients. Recurrence of the curvature and penile hypo-aesthesia is uncommon (~10%) and the risk of post-operative ED is low. Penile shortening is the most commonly reported outcome of these procedures. Shortening of 1-1.5 cm has been reported for 22-69% of patients, which is rarely the cause of post-operative sexual dysfunction and patients may perceive the loss of length as greater than it actually is. It is therefore strongly advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used (Table 31).

As mentioned above, there are multiple techniques with small modifications and all of them have been reported in retrospective studies, most of them without comparison between techniques and therefore the level of evidence is not sufficient to recommend one method over another.

Table 31: Results of tunical shortening procedures for PD (data from different, non-comparable studies) [1059, 1170-1197]

	Tunical shortening procedures				
	Nesbit	**Modified Nesbit**	**Yachia**	**16-dot / mod16-dot**	**Simple plication**
No. of patients/studies	652 / 4	387 / 5	150 / 6	285 / 5	1068 / 18
Significant penile shortening (%)*†	8.7% (5-39)	3.2% (0-13)	3.5% (0-10)	5.9% (0-6)	8.9% (0-55)
Any penile shortening (%)*	21.8% (9-39)	58.% (23-74)	69% (47-97)	44.6% (40-52)	33.4% (0-90)
Penile straightening (%)*	88.5% (86-100)	97.6% (92-100)	95.5% (93-100)	96.9% (95-100)	94.7% (85-100)
Post-operative *de novo* ED (%)*	6.9% (0-17)	3% (0-13)	9.6% (0-13)	3.8% (0-13)	8.1% (0-38)
Penile hypoesthesia (%)*	11. 8% (2-60)	5.6% (0-31)	1% (0-3)	8.2% (6-13)	9% (0-47)
Overall satisfaction (%)*	83.5% (76-88)	95.4% (87-100)	86.8% (78-100)	94% (86-100)	86.4% (52-100)
Follow-up (months)*	(69-84)	(19-42)	(10-24)	(18-71)	(12-141)

**Data are expressed as weighted average. † Defined as > 30 degrees of curvature. Ranges are in parentheses. ED = Erectile dysfunction.*

8.2.3.2.2 Tunical lengthening procedures

Tunical lengthening surgery is preferable in patients with significant penile shortening, severe curvature and/or complex deformities (hourglass or hinge) but without underlying ED. The definition of severe curvature has been proposed to be > 60°, although no studies have validated this threshold. However, it may be used as an informative guide for patients and clinicians in surgical counselling and planning, although there is no unanimous consensus based on the literature that such a threshold can predict surgical outcomes (Panel expert consensus opinion). On the concave side of the penis, at the point of maximum curvature, which usually coincides with the location of the plaque, an incision is made, creating a defect in the albuginea that is

covered with a graft. Complete plaque removal or plaque excision may be associated with higher rates of post-operative ED due to venous leak, but partial excision in cases of florid calcification may be permissible [1201, 1202]. Patients who do not have pre-operative ED should be informed of the significant risk of post-operative ED of up to 50% [1154].

Since 1974, when the first study using dermal grafting to treat PD was published [1203], a large number of different grafts have been used. The ideal graft should be resistant to traction, easy to suture and manipulate, flexible (not too much, to avoid aneurysmal dilations), readily available, cost-effective, and morbidity should be minimal, especially when using autografts. No graft material meets all of these requirements. Moreover, the studies performed did not compare different types of grafts and biomaterials and were often single-centre retrospective studies so there is not a single graft that can be recommended for surgeons [1204]. Grafting procedures are associated with long-term ED rates as high as 50%. The presence of pre-operative ED, the use of larger grafts, age > 60 years, and ventral curvature are considered poor prognostic factors for good functional outcomes after grafting surgery [1157]. Although the risk for penile shortening appears to be less than that compared to the Nesbit, Yachia or plication procedures, it is still an issue and patients must be informed accordingly [1156]. Higher rates (3-52%) of penile hypo-aesthesia have also been described after these operations, as damage of the neurovascular bundle with dorsal curves (in the majority) is inevitable. A recent prospective study showed that 21% of patients had some degree of sensation loss at 1 week, 21% at 1 month, 8% at 6 months, and 3% at 1 year [1205]. The use of geometric principles introduced by Egydio may help to determine the exact site of the incision, and the shape and size of the defect to be grafted [1206].

Grafts for PD surgery can be classified into four types (Table 31) [1049]:

- Autografts: taken from the individual himself, they include the dermis, vein, temporalis fascia, fascia lata, tunica vaginalis, tunica albuginea and buccal mucosa.
- Allografts: also of human origin but from a deceased donor, including the pericardium, fascia lata and dura mater.
- Xenografts: extracted from different animal species and tissues, including bovine pericardium, porcine small intestinal submucosa, bovine and porcine dermis, and TachoSil® (matrix of equine collagen).
- Synthetic grafts: these include Dacron® and Gore-Tex®.

All the autologous grafts have the inconvenience of possible graft harvesting complications. Dermal grafts are commonly associated with veno-occlusive ED (20%) due to lack of adaptability, so they have not been used in contemporary series [1203, 1204, 1207-1217]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The saphenous vein has been the most commonly used vein graft [1218-1233]. For some extensive albuginea defects, more than one incision may be needed. Tunica albuginea grafts have perfect histological properties but have some limitations: the size that can be harvested, the risk of weakening penile support and making future procedures (penile prosthesis implantation) more complicated [1234-1236]. Tunica vaginalis is easy to harvest and has little tendency to contract due to its low metabolic requirements, although better results can be obtained if a vascular flap is used [1237-1241]. Under the pretext that by placing the submucosal layer on the corpus cavernosum the graft feeds on it and adheres more quickly, the buccal mucosal graft has recently been used with good short-term results [1242-1248].

Cadaveric dura mater is no longer used due to concerns about the possibility of infection [1249, 1250]. Cadaveric pericardium (Tutoplast©) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [1139, 1202, 1213, 1251, 1252]. Cadaveric or autologous fascia lata or temporalis fascia offers biological stability and mechanical resistance [1253-1255].

Xenografts have become more popular in recent years. Small intestinal submucosa (SIS), a type I collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine, has been shown to promote tissue-specific regeneration and angiogenesis, and supports host cell migration, differentiation and growth of endothelial cells, resulting in tissue structurally and functionally similar to the original [1256-1265]. As mentioned above, pericardium (bovine, in this case) has good traction resistance and adaptability, and good host tolerance [1233, 1266-1269]. Grafting by collagen fleece (TachoSil©) in PD has some major advantages such as decreased operating times, easy application and an additional haemostatic effect [1270-1275].

It is generally recommended that synthetic grafts, including polyester (Dacron®) and polytetrafluoroethylene (Gore-Tex®) are avoided, due to increased risks of infection, secondary graft inflammation causing tissue fibrosis, graft contractures, and possibility of allergic reactions [1178, 1276-1279].

Some authors recommend post-operative penile rehabilitation to improve surgical outcomes. Some studies have described using VED and PTT to prevent penile length loss of up to 1.5 cm [1280]. Daily nocturnal administration of PDE5I enhances nocturnal erections, encourages perfusion of the graft, and may minimise post-operative ED [1281]. Massages and stretching of the penis have also been recommended once wound healing is complete.

Table 32: Results of tunical lengthening procedures for PD (data from different, non-comparable studies) [1139, 1178, 1202, 1203, 1207-1275, 1282, 1283]

	Year of publication	No. of patients / studies	Success (%)*	Penile shortening (%)*	*De novo* ED (%)*	Follow-up (mo)*
Autologous grafts						
Dermis	1974-2019	718 / 12	81.2% (60-100)	59.9% (40-75)	20.5% (7-67)	(6-180)
Vein grafts	1995-2019	690 / 17	85.6% (67-100)	32.7% (0-100)	14.8% (0-37)	(12-120)
Tunica albuginea	2000-2012	56 / 3	85.2% (75-90)	16.3% (13-18)	17.8% (0-24)	(6-41)
Tunica vaginalis	1980-2016	76 / 5	86.2% (66-100)	32.2% (0-83)	9.6% (0-41)	(12-60)
Temporalis fascia / Fascia lata	1991-2004	24 / 2	100%	0%	0%	(3-10)
Buccal mucosa	2005-2016	137 / 7	94.1% (88-100)	15.2% (0-80)	5.3% (0-10)	(12-45)
Allografts (cadaveric)						
Pericardium	2001-2011	190 / 5	93.1% (56-100)	23.1% (0-33)	37.8% (30-63)	(6-58)
Fascia lata	2006	14 / 1	78.6%	28.6%	7.1%	31
Dura matter	1988-2002	57 / 2	87.5%	30%	17.4% (15-23)	(42-66)
Xenografts						
Porcine SIS	2007-2018	429 / 10	83.9% (54-91)	19.6% (0-66)	21.9% (7-54)	(9-75)
Bovine pericardium	2002-2020	318 / 6	87.4% (76.5-100)	20.1% (0-79.4)	26.5% (0-50)	(14-67)
Bovine dermis	2016	28 / 1	93%	0%	25%	32
Porcine dermis	2020	19 / 1	73.7%	78.9%	63%	85
TachoSil®	2002-2020	529 / 7	92.6% (83.3-97.5)	13.4% (0-93)	13% (0-21)	(0-63)

**Data are expressed as weighted average. Ranges are in parentheses.*
ED = Erectile dysfunction; SIS = Small intestinal submucosa.

The results of tunical shortening and lengthening approaches are presented in Tables 30 and 31. It must be emphasised that there have been no RCTs comparing surgical outcomes in PD. The risk of ED seems to be greater for penile lengthening procedures [1057]. Recurrent curvature is likely to be the result of failure to wait until the disease has stabilised, re-activation of the condition following the development of stable disease, or the use of early re-absorbable sutures (e.g., Vicryl) that lose their strength before fibrosis has resulted in acceptable strength of the repair. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed absorbable sutures (e.g., polydioxanone) should be used. With non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, but this issue may be alleviated by the use of slowly re-absorbable sutures (e.g., polydioxanone) [1165]. Penile numbness is a potential risk of any surgical procedure, involving mobilisation of the dorsal neurovascular bundle. This is usually a temporary neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure, or the association with (albeit rare) ventral [1156].

8.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with concomitant ED not responding to conventional medical therapy (PDE5I or intracavernous injections of vasoactive agents) [1057]. Although inflatable prostheses (IPPs) have been considered more effective in the general population with ED, some studies support the use of malleable prostheses in these patients with similar satisfaction rates [1057, 1284, 1285]. The evidence suggests that there is no real difference between the available IPPs [1286]. Surgeons can and should advise on which type of prosthesis best suits the patient but it is the patient who should ultimately choose the prosthesis to be implanted [692].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion [1231, 1287]. If the curvature after placement of the prosthesis is < 30° no further action is indicated, since

the prosthesis itself will act as an internal tissue expander to correct the curvature during the subsequent 6-9 months. If, the curvature is > 30°, the first-line treatment would be modelling with the prosthesis maximally inflated (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) [1288, 1289]. If, after performing this manoeuvre, a deviation > 30° persists, subsequent steps would be incision with collagen fleece coverage or without (if the defect is small, it can be left uncovered) or plaque incision and grafting [1290-1295]. However, the defect may be covered if it is larger, and this can be accomplished using grafts commonly used in grafting surgery (described above) which prevent herniation and recurrent deformity due to the scarring of the defect [1296]. The risk of complications (infection, malformation, etc.) is not increased compared to that in the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis [1288].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the "sliding" technique has been considered [1297]. Although the "sliding" technique is not recommended due to reported cases of glans necrosis because of the concomitant release of the neurovascular bundle and urethra, new approaches for these patients have been recently described, such as the MoST (Modified Sliding Technique), MUST (Multiple-Slit Technique) or MIT (Multiple-Incision Technique) techniques, but these should only be used by experienced high-volume surgeons and after full patient counselling [1298-1301].

While patient satisfaction after IPP placement in the general population is high, satisfaction rates have been found to be significantly lower in those with PD. Despite this, depression rates decreased after surgery in PD patients (from 19.3-10.9%) [1302]. The main cause of dissatisfaction after PPI in the general population is a shortened penile length. Therefore, patients with PD undergoing PP surgery must be counselled that the prostheses are not designed to restore the previous penile length [1302, 1303].

8.2.3.2.4 Summary of evidence for surgical treatment of Peyronie's disease

Summary of evidence	LE
Surgery for PD should only be offered in patients with stable disease with functional impairment.	2b
In patients with concomitant PD and ED without response to medical treatment, penile prosthesis implantation with or without additional straightening manoeuvres is the technique of choice.	2a
In other cases, factors such as penile length, rigidity of erection, degree of curvature, presence of complex deformities and patient choice must be taken into account to decide on a tunical shortening or lengthening technique.	3

8.2.3.2.5 Recommendations for surgical treatment of penile curvature

Recommendations	Strength rating
Perform surgery only when Peyronie's disease (PD) has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms, and intercourse is compromised due to the deformity.	Strong
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, less severe curvatures and absence of complex deformities (hourglass or hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hourglass or hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.	Weak
Use the sliding techniques with extreme caution, as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional procedure (modelling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

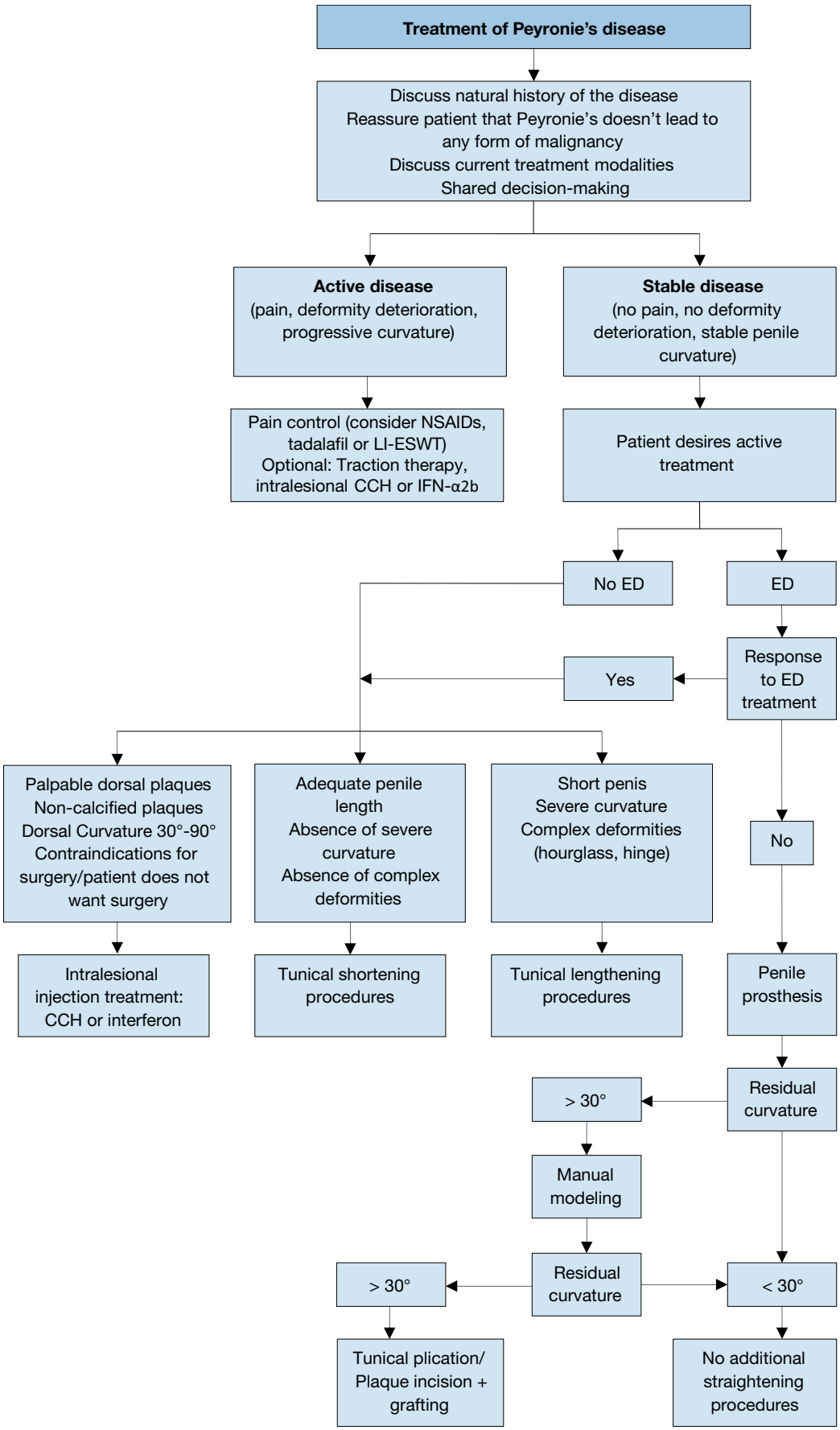
8.2.3.3 Treatment algorithm

As mentioned above, in the active phase of the disease, most therapies are experimental or with low evidence. In cases of pain, LI-ESWT, tadalafil and NSAIDs can be offered. In cases of curvature or penile shortening, traction therapy has demonstrated good responses.

When the disease has stabilised, intralesional treatments (mainly CCH) or surgery may be used. Intralesional treatments may reduce the indications for surgery or change the technique to be performed but only after full patient counselling, which should also include a cost-benefit discussion with the patient.

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of curvature and erectile function status. In non-complex and non-severe deformities, tunical shortening procedures are acceptable and are usually the method of choice. This is typically the case for CPC. If severe curvature or complex deformation is present (hourglass or hinge), or if the penis is significantly shortened in patients with good erectile function (preferably without pharmacological treatment), then tunical lengthening is feasible, using any of the grafts previously mentioned. If there is concomitant ED, which is not responsive to pharmacological treatment, the best option is the implantation of a penile prosthesis, with or without a straightening procedure over the penis (modelling, plication, incision or excision with or without grafting). The treatment algorithm is presented in Figure 11.

Figure 11: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT = Low-intensity extracorporeal shockwave treatment; NSAIDs = non-steroidal anti-inflammatory drugs; CCH = Collagenase Clostridium histolyticum; IFN-α2b = Interferon-α2b.

9. PRIAPISM

Evidence Acquisition and limitations
The Panel conducted systematic reviews on the medical and surgical management of ischaemic and non-ischaemic priapism and a dedicated systematic review on the overall management of priapism related to sickle cell disease. The results of these systematic reviews are presented below in the guidelines and the limitations of the studies that were assessed are highlighted.

Most studies had the same limitations and methodological bias: lack of published protocols, retrospective and usually single-arm design, lack of randomisation and blinding, incomplete outcome data, and selective reporting. Additionally, most studies included small numbers of patients, reported non-standardised patient characteristics, and had short (or even unreported) follow-up times and, in general, they reflected single-unit practices.

The definitions of priapism and outcomes (such as success and related complications) were inconsistent across the literature and few of the trials met the clear definitions that were set by the Panel for use in the systematic reviews. Hence, any attempt to draw clinically meaningful conclusions and offer evidence-based guidance based on systematic assessment of the literature was a challenging task. These limitations highlight the urgent need for clear and commonly accepted definitions of conditions and outcomes that should be used by researchers in the future so that robust evidence can be developed to support relevant guidelines and clinical practice recommendations.

The Panel acknowledged the evidence-related limitations, and in accordance with the GRADE approach endorsed by the European Association of Urology Guidelines Office, also took into consideration the benefits/harms balance and the patient ideals, views and preferences prior to finalising the relevant recommendations (for/against, weak/strong).
Priapism is a persistent or prolonged erection in the absence of sexual stimulation that fails to subside. It can be divided into ischaemic, non-ischaemic and stuttering priapism.

9.1 Ischaemic (Low-Flow or Veno-Occlusive) Priapism

9.1.1 ***Epidemiology, aetiology, pathophysiology and Diagnosis***

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [1304]. Ischaemic priapism is the most common subtype of priapism, accounting for > 95% of all episodes [1304, 1305]. It presents as a painful rigid erection that is characterised clinically by absent or reduced intracavernous arterial inflow, although proximally there is a compensated high velocity picture with little flow distally [1306]. In ischaemic priapism, there are time-dependent metabolic alterations within the corpus cavernosum progressively leading to hypoxia, hypercapnia, glucopenia and acidosis [1307, 1308].

Ischaemic priapism that lasts beyond 4 hours is similar to a compartment syndrome and characterised by the development of ischaemia within the closed space of the corpora cavernosa, which severely compromises the cavernosal circulation. Emergency medical intervention is required to minimise irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and the development of permanent erectile dysfunction (ED) [1309, 1310]. The duration of ischaemic priapism represents the most significant predictor for the development of ED. In this context, interventions beyond 48-72 hours of onset may help to relieve the erection and pain, but have little clinical benefit in preventing long-term ED [1311].

Histological analysis of corporal smooth muscle biopsies shows that at 12 hours, there are features of interstitial oedema, progressing to destruction of the sinusoidal endothelium, exposure of the basement membrane and thrombocyte adherence by 24 hours. At 48 hours, thrombi in the sinusoidal spaces and smooth muscle necrosis with fibroblast-like cell transformation are evident [1312]. This implies that by 48 hours there appears to be smooth muscle necrosis and irreversibility of these ischaemic changes. A case-control study comparing corporal biopsies from patients with priapism lasting 48-72 hours with control penile tissues retrieved from autopsies demonstrated a significantly lower percentage of smooth muscle fibres, with an increase in elastic fibres and collagen [1309, 1313].

No specific pathophysiological causes of ischaemic priapism can be identified in most cases [1304, 1314], although the common aetiological factors include sickle cell disease (SCD), haematological dyscrasias, neoplastic syndromes, and several pharmacological agents (e.g., intracavernosal PGE1 therapy) (Table 32). Ischaemic priapism may occur (0.4-35%) after intracavernosal injection of erectogenic agents [585, 1304, 1309, 1315, 1316]. The risk is higher with papaverine-based combinations [1317], while the risk of priapism is < 1% following prostaglandin E1 injection [1318].

Second-generation antipsychotics (33.8%), other medications (11.3%), and alpha-adrenergic antagonists (8.8%) accounted for the greatest percentage of published drug-induced priapism cases [1319]. Isolated cases of priapism have been described in men who have taken PDE5Is [1304]. A recent study from the FDA Adverse Reporting System Public Dashboard showed that PDE5Is-induced priapism accounted for only 2.9% of drug-induced priapism. However, most of these men also had other risk factors for priapism, and it is unclear whether PDE5Is per se can cause ischaemic priapism [1304]. Since most men who experience priapism following PDE5I treatment have additional risk factors for ischaemic priapism, PDE5Is use is usually not regarded as a risk factor in itself. In terms of haemoglobinopathies, SCD is the most common cause of priapism in childhood, accounting for 63% of cases. It is the primary aetiology in 23% of adult cases [1318], and men with SCD have a lifetime probability of 29-42% of developing ischaemic priapism [1318, 1320, 1321] (LE: 4).

Mechanisms of SCD-associated priapism may involve derangements of several signalling pathways in the penis, resulting in disinhibited vasorelaxation of the cavernous smooth muscle by nitric oxide synthase (NOS) and Rho-associated protein kinase (ROCK) signalling, and increased oxidative stress associated with nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated signalling. Excessive adenosine and up-regulation of opiorphins in response to hypoxia reduce PDE5 gene expression and activity and impair NO bioavailability in the penis. Excessive oxidative/nitrosative stress and decreased activity of the RhoA/Rho-kinase contractile pathway further promotes priapism. Contrary to traditional belief, maintenance of physiological testosterone levels does not cause priapism, but rather preserves penile homeostasis and promotes normal erectile function [1322, 1323]. Testosterone deficiency is considered a controversial risk factor: it is prevalent in patients with SCD, but recent evidence indicates that it is not a risk factor *per se* for priapism [1324].

Priapism resulting from metastatic or regional infiltration by tumour is rare and usually reflects an infiltrative process, more often involving the bladder and prostate as the primary cancer sites [1325]. In a recent large retrospective study including 412 men with ischaemic priapism, eleven (3.5%) had malignant priapism, of which seven cases were a consequence of local invasion while the others were secondary to haematological malignancy [1326]. The conventional therapeutic recommendations for pharmacological treatment are unlikely to be effective and all of these men should have MRI of the penis and be offered supportive care and medical intervention for their primary cancer. In selected cases where palliative treatment options fail to control penile pain, a palliative penectomy can be considered.

Partial priapism, or idiopathic partial segmental thrombosis of the corpus cavemosum, is a rare condition. It is often classified as a subtype of priapism limited to a single crura without ischaemia, but rather a thrombus is present within the corpus cavernosum. Its aetiology is unknown, but bicycle riding, trauma, drug use, sexual intercourse, haematological diseases and α-blockers intake have all been associated with partial segmental thrombosis [1327]. The presence of a congenital web within the corpora is also a risk factor [1328].

Table 33: Aetiological factors for the development of priapism

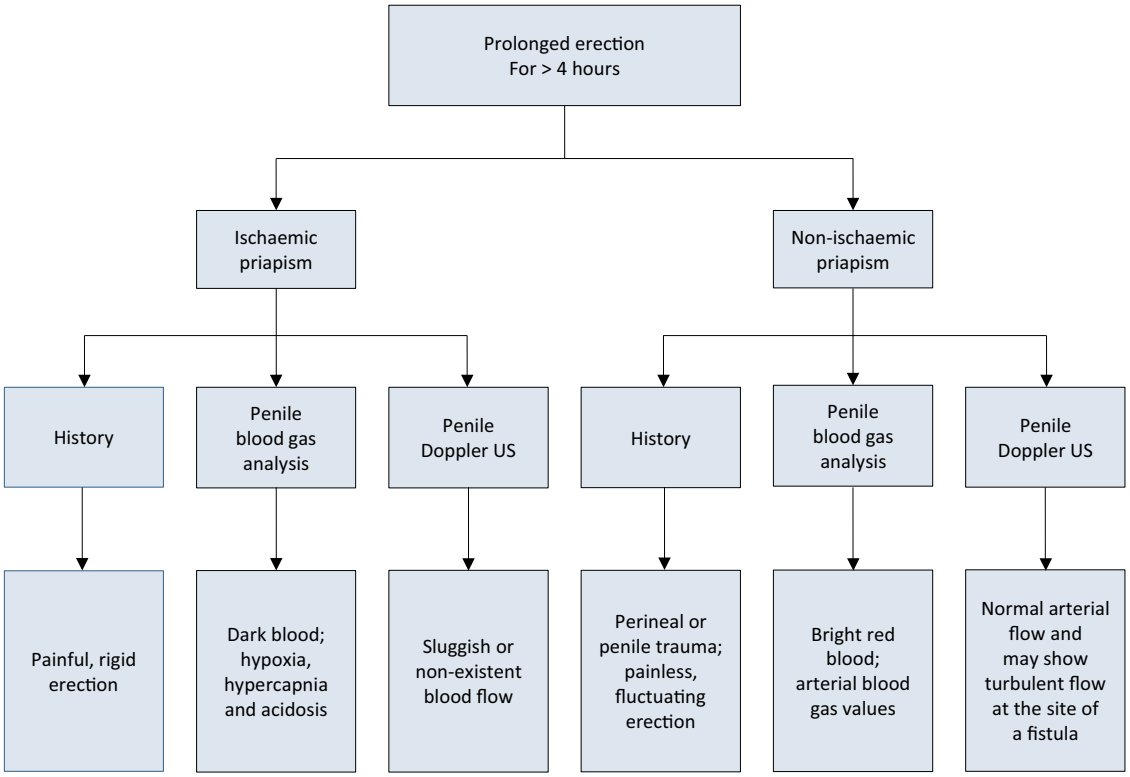
Idiopathic	Haematological dyscrasias Vascular and other disorders	Infections (toxin-mediated)	Metabolic disorders	Neurogenic disorders	Neoplasms (metastatic or regional infiltration)	Medications
	- SCD, - thalassemia, - leukaemia; - multiple myeloma, - haemoglobin Olmsted variant, - fat emboli during hyperalimentation, - haemodialysis, - glucose-6-phosphate dehydrogenase deficiency, - factor V Leiden mutation - vessel vasculitis (e.g., Henoch-Schönlein purpura; Behçet's disease; anti-phospholipid antibodies syndrome)	- scorpion sting, - spider bite, - rabies, - malaria	- amyloidosis, - Fabry's disease, - gout	- syphilis, - spinal cord injury, - cauda equina syndrome, - autonomic neuropathy, - lumbar disc herniation, - spinal stenosis, - cerebrovascular accident, - brain tumour, - spinal anaesthesia	- prostate, - urethra, - testis, - bladder, - rectal, - lung, - kidney	- Vasoactive erectile agents (i.e., papaverine, phentolamine, prostaglandin E1/ alprostadil, combination of intracavernous therapies) - α-adrenergic receptor antagonists (i.e., prazosin, terazosin, doxazosin and tamsulosin) - Anti-anxiety agents (hydroxyzine) - Anticoagulants (heparin and warfarin) - Antidepressants and antipsychotics (i.e., trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thiorizadine, phenothiazines and methylphenidate) - Antihypertensives (i.e., hydralazine, guanethidine and propranolol) - Hormones (i.e., gonadotropin-releasing hormone and testosterone) - Recreational drugs (i.e., alcohol, marijuana, cocaine [intranasal and topical], and crack, cocaine)

9.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

Summary of evidence	LE
Ischaemic priapism is the most common type, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in most patients, while sickle cell disease is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (about 5%) after intracavernous injections of papaverine-based combinations, while it is rare (< 1%) after prostaglandin E1 monotherapy.	2a
Priapism is rare in men who have taken Phosphodiesterase Type 5 Inhibitors, with only sporadic cases reported.	4

9.1.2 *Diagnostic evaluation*

Figure 12: Differential diagnosis of priapism


Prolonged erection
For > 4 hours
Ischaemic priapism
Non-ischaemic priapism
History
Penile blood gas analysis
Penile Doppler US
History
Penile blood gas analysis
Penile Doppler US
Painful, rigid erection
Dark blood; hypoxia, hypercapnia and acidosis
Sluggish or non-existent blood flow
Perineal or penile trauma; painless, fluctuating erection
Bright red blood; arterial blood gas values
Normal arterial flow and may show turbulent flow at the site of a fistula

9.1.2.1 *History*

Taking a comprehensive history is critical in priapism diagnosis and treatment [1304, 1329]. The medical history must specifically enquire about SCD or any other haematological abnormality [1330, 1331] and a history of pelvic, genital or perineal trauma. The sexual history must include the duration of the erection, the presence and degree of pain, prior drug treatment, history of priapism and erectile function prior to the last priapism episode (Table 33). The history can help to determine the underlying priapism subtype (Table 34). Ischaemic priapism is classically associated with progressive penile pain and the erection is rigid. However, non-ischaemic priapism is often painless and the erections often fluctuate in rigidity.

Table 34: Key points in the history for a priapism patient (adapted from Broderick *et al.* [1304])

Duration of erection
Presence and severity of pain
Previous episodes of priapism and methods of treatment
Current erectile function, especially the use of any erectogenic therapies prescription or nutritional supplements
Medications and recreational drug use
Sickle cell disease, haemoglobinopathies, hypercoagulable states, vessel vasculitis
Trauma to the pelvis, perineum or penis

9.1.2.2 *Physical examination*

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient complains of severe pain. Pelvic examination may reveal an underlying pelvic or genitourinary malignancy [1326].

9.1.2.3 *Laboratory testing*

Laboratory testing should include a complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [1304, 1329].

A genome-wide association study on Brazilian patients identified four single nucleotide polymorphisms in LINC02537 and NAALADL2 significantly associated with priapism, although testing is not routinely recommended in clinical practice [1332].

Aspiration of blood from the corpora cavernosa usually reveals dark ischaemic blood (Table 33) (LE: 2b). Blood gas analysis is essential to differentiate between ischaemic and non-ischaemic priapism (Table 34). Further laboratory testing should be directed by the history, clinical examination and laboratory findings. These may include specific tests (e.g., haemoglobin electrophoresis) for diagnosis of SCD or other haemoglobinopathies.

9.1.2.4 Penile imaging

Colour Doppler US of the penis and perineum is recommended after clinical diagnosis and can differentiate ischaemic from non-ischaemic priapism as an alternative or adjunct to blood gas analysis [1306, 1333-1335] (LE: 2b). Colour Doppler US can identify the presence of the fistula as a blush with 100% sensitivity and 73% specificity [1335].

Ultrasound scanning of the penis should be performed before corporal blood aspiration in ischaemic priapism to prevent aberrant blood flow which can mimic a non-ischaemic picture or reperfusion picture after intervention for low-flow priapism [1336].

Following Colour Doppler US there will be an absence of blood flow in the cavernosal arteries in ischaemic priapism. Return of the cavernous artery waveform indicates successful detumescence [1304, 1335, 1337]. After aspiration, reactive hyperaemia may develop with a high arterial flow proximally that may be misleading and result in the diagnosis of non-ischaemic priapism.

Penile MRI can be used in the diagnostic evaluation of priapism and may be helpful in selected cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In particular, in cases of refractory priapism or delayed presentation (> 48 hours), smooth muscle viability can be indirectly assessed. In a prospective study of 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, when correlated with corpus cavernosum biopsies [1336]. In this study, all patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up with the non-viable group being offered an early prosthesis.

Table 35: Key findings in priapism (adapted from Broderick *et al.* [1304])

	Ischaemic priapism	Non-ischaemic priapism
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Haematological abnormalities	Sometimes	Seldom
Recent intracavernosal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Typically

Table 36: Typical blood gas values (adapted from Broderick *et al.* [1304])

Source	pO_2 (mmHg)	pCO_2 (mmHg)	pH
Normal arterial blood (room air) (similar values are found in arterial priapism)	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

9.1.2.5 Recommendations for the diagnosis of ischaemic priapism

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
For laboratory testing, include complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile. Directed further laboratory testing should be performed depending upon history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	Strong

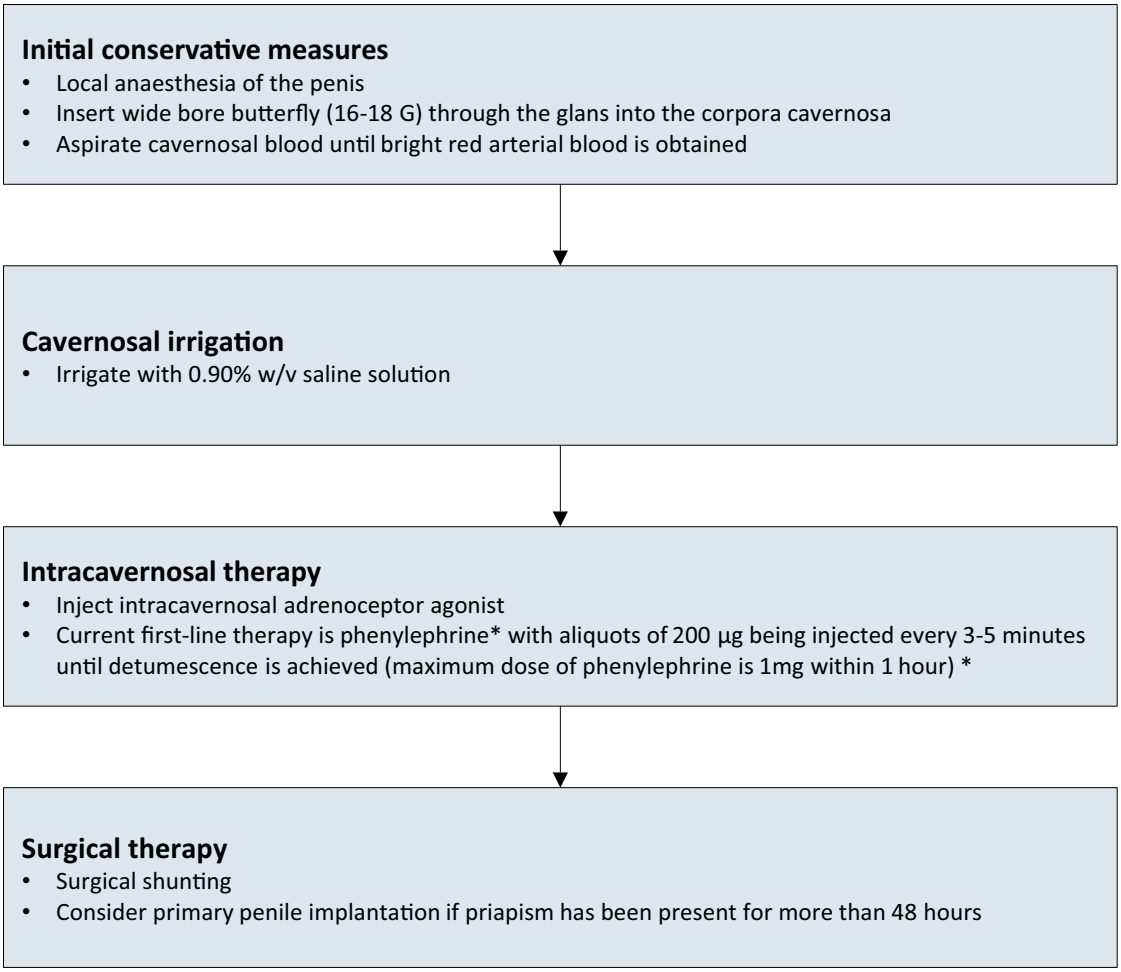
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum before aspiration to differentiate between ischaemic and non-ischaemic priapism.	Strong
In cases of prolonged ischaemic priapism or refractory priapism, magnetic resonance imaging of the penis may be used as an adjunct to predict smooth muscle viability.	Weak
Perform selected pudendal arteriogram when embolisation is planned for the management of non-ischaemic priapism.	Strong

*9.1.3 **Disease management***

Acute ischaemic priapism is a medical emergency. Urgent intervention is mandatory and should follow a stepwise approach. The aim of any treatment is to restore penile detumescence, without pain, in order to prevent corporal smooth muscle fibrosis and subsequent ED.

Figure 13: Medical and surgical management of ischaemic priapism

The treatment is sequential and physicians should move on to the next stage if treatment fails.


Initial conservative measures
• Local anaesthesia of the penis
• Insert wide bore butterfly (16-18 G) through the glans into the corpora cavernosa
• Aspirate cavernosal blood until bright red arterial blood is obtained
Cavernosal irrigation
• Irrigate with 0.90% w/v saline solution
Intracavernosal therapy
• Inject intracavernosal adrenoceptor agonist
• Current first-line therapy is phenylephrine* with aliquots of 200 µg being injected every 3-5 minutes until detumescence is achieved (maximum dose of phenylephrine is 1mg within 1 hour) *
Surgical therapy
• Surgical shunting
• Consider primary penile implantation if priapism has been present for more than 48 hours

(*) Dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease. Monitoring of pulse and blood pressure is advisable in all patients during administration and for one hour afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

9.1.3.1 Medical Management

Evidence Acquisition

The studies that were identified after abstract screening and used for this literature review pertaining to medical management are reported in the table in Appendix 1. Most of these studies were retrospective case series without an available protocol. Additionally, several limitations were encountered during their assessment, including small study samples, unclear definitions of conditions, interventions and outcomes,

short or no reported follow-up and selective reporting of outcomes. As such, providing clinicians with clear recommendations based on robust evidence was not possible. Based on the studies included in the Panel's systematic review, medical management of priapism demonstrates a wide range of effectiveness, although it seems that sexual dysfunction and complication rates in medical management responders were not too high, when reported. It should be emphasised that most patients included in the surgical management studies that are discussed below represent medical non-responders. The selection bias that by definition existed in the surgical management in these single-arm studies makes the estimation of true effectiveness of medical intervention difficult to quantify.

9.1.3.1.1 First-line treatments

First-line medical treatments of ischaemic priapism of more than 4 hours duration are strongly recommended before any surgical treatment (LE: 4). Conversely, first-line treatments initiated beyond 48 hours, while relieving priapism, have little documented benefit in terms of long-term potency preservation (LE: 4). This is likely to be the consequence of irreversible smooth muscle damage that begins to be established by approximately 48 hours of tissue hypoxia [1309-1311]. An in-vitro model of priapism has shown that there is window of opportunity for therapeutic intervention beyond which the recovery of functional erectile tissue is unlikely due to irreversible smooth muscle cell dysfunction [1307]. In line with this finding it has been shown in a series of 50 patients with low-flow priapism who were successfully treated and followed-up for a mean 66 months, those with priapism lasting for more than 48 hours had a significant risk of ED [1309].

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [1304]. However, there is limited evidence for the benefit of such measures and they may even exacerbate crisis in SCD patients. Success rates of these conservative measures alone have been rarely reported. In a small series, for instance, cold water enemas have been reported to induce detumescence in six out of ten cases [1338]. In another study 24.5% of 122 patients achieved detumescence following priapic episodes lasting for more than 6 hours by cooling of the penis and perineum, and walking upstairs [1320]. In SCD patients with priapism, it is recommended that the urology team works closely with the haematology team to optimise patient management.

Partial priapism usually resolves spontaneously with analgesic treatment while surgical intervention is rarely needed [1339].

9.1.3.1.2 Penile anaesthesia/analgesia

It is possible to perform blood aspiration and intracavernous injection of a sympathomimetic agent without any anaesthesia. However, anaesthesia may be necessary when there is severe penile pain. While it is recognised that the anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia facilitates subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:

- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

9.1.3.1.3 Aspiration ± irrigation with 0.9% w/v saline solution

The first intervention for an episode of priapism lasting more than 4 hours consists of corporal blood aspiration (LE: 4) to drain the stagnant blood from the corporal bodies, making it possible to relieve the compartment-syndrome-like condition within the corpus cavernosum. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access to the lateral aspect of the proximal penile shaft, using a 16 or 18 G angio-catheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain blood from the corpus cavernosum (LE: 4).

Some clinicians advocate using two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [1320] (LE: 4). Aspiration should be continued until bright red, oxygenated blood is aspirated (LE: 4).

Several case series have reported the outcomes from first-line treatments, although in most cases, aspiration and irrigation were combined with intracavernosal injection of sympathomimetic agents, thus making it difficult to draw conclusions about the success rate of aspiration + irrigation alone. In a RCT, 70 patients with ischaemic priapism secondary to intracavernosal injection and lasting more than 6 hours were treated with aspiration plus saline irrigation at different temperatures [1320]. The authors reported an 85% success rate with the optimum results achieved using a 10°C saline infusion after blood aspiration.

This approach has up to a 30% chance of resolving the priapism. There are insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone (LE: 4).

9.1.3.1.4 Aspiration ± irrigation with 0.9% w/v saline solution in combination with intracavernous injection of pharmacological agents.

This combination is currently considered the standard of care for treatment of ischaemic priapism [1304, 1340, 1341] (LE: 4). Pharmacological agents include sympathomimetic drugs or α-adrenergic agonists. Intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80% [1304, 1340, 1342-1349] (LE: 2b). The use of intracavernous adrenaline injection alone has also been sporadically reported [1350]. A literature review from the AUA reported that the use of a sympathomimetic agent combined with prior intracavernosal aspiration or irrigation had a resolution rate of 77% as compared with 58% in those who had a sympathomimetic injection alone [1341].

Phenylephrine

Adrenergic agonists act on the post-synaptic α-1-adrenergic receptors to stimulate cavernosal smooth muscle and arteriolar vasoconstriction, with a reduction in arteriolar inflow to the corporal bodies and smooth muscle contraction [1351]. Moreover, this class of drug also increases venous outflow through β2-adrenergic receptor activity [1348].

Phenylephrine is a selective α-1-adrenergic receptor agonist that has been observed in small case series to be effective at producing detumescence in priapism, when given as an intracavernosal injection, with few adverse effects [1348, 1352]. Therefore, phenylephrine is the recommended adrenergic agonist drug of choice due to its high selectivity for the α-1-adrenergic receptor, without concomitant β-mediated inotropic and chronotropic cardiac effects [1342, 1346, 1347] (LE: 4).

Phenylephrine is diluted in normal saline to a concentration of 100-500 µg/mL. Usually, 200 µg are given every three to five minutes directly into the corpus cavernosum. The maximum dosage is 1 mg within 1 hour (LE: 4). A lower concentration or volume is applicable for children and patients with severe cardiovascular diseases (LE: 4).

Higher doses of phenylephrine have been used in small retrospective case series [1346, 1347, 1353, 1354] without any adverse events, but further trials are needed to substantiate the efficacy of higher doses. There are *in-vitro* data suggesting that higher doses of phenylephrine are unlikely to be beneficial when conventional doses have failed because there is already significant apoptosis of the cavernosal smooth muscle [1355].

Phenylephrine has potential cardiovascular adverse effects [1304, 1340, 1342, 1343, 1346, 1347] and it is recommended that blood pressure and pulse are monitored every fifteen minutes for 1 hour after injection. This is particularly important in older men with pre-existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpus cavernosum massaged to facilitate drug distribution.

The potential treatment-related adverse effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations and sporadic subarachnoid haemorrhage [380]. Monitoring of blood pressure and pulse should be performed during intracavernous administration of sympathomimetic agents.

Given that intracavernous sympathomimetic agents can cause hypertension, the Panel is of the opinion that these agents are contraindicated in patients with malignant or poorly controlled hypertension, as there are case reports of significant cardiovascular and neurological complications following the use of these pharmacological agents for priapism [1343, 1356, 1357]. Similarly, there are data suggesting that sympathomimetic agents cause a hypertensive crisis when given with monoamine oxidase inhibitors, hence these medications should not be used together [1358] (LE: 4).

Etilephrine

Etilephrine is also an adrenergic agonist but directly stimulates both α and β adrenergic receptors [1341]. Most of the literature describing the use of etilephrine for treatment of priapism is related to men with SCD but there are small retrospective case series that have reported its benefits for priapism secondary to iatrogenic causes [1359, 1360]. Etilephrine is the second most widely used sympathomimetic agent, administered by intracavernous injection at a concentration of 2.5 mg in 1-2 mL normal saline [1343] (LE: 3).

Methylene blue
Methylene blue is a guanylate cyclase inhibitor, that may be a potential inhibitor of endothelial-mediated cavernous smooth muscle relaxation. Small retrospective case series have reported its successful use for treating short-term pharmacologically-induced priapism [1361, 1362] (LE: 3). Methylene blue, 50-100 mg [1361], should be injected intracavernously and left for five minutes. It is then aspirated and the penis compressed for an additional five minutes [1362]. Treatment-related adverse effects include a transient burning sensation and blue discolouration of the penis.

Adrenaline
Adrenaline produces both α-adrenergic receptor agonist and α-adrenergic receptor activity. Intracavernosal adrenaline (2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period [1350]) has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. The limited literature [1350, 1363] suggests that adrenaline can achieve detumescence in short-term priapism, with one small case series reporting a success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections [1350, 1363] (LE: 3).

β-2-agonists
Oral terbutaline is a β-2-agonist with minor β-1 effects and some α-agonist activity. A dose of 5 mg has been suggested to treat prolonged erections lasting more than 2.5 hours, after intracavernous injection of vasoactive agents, although the mechanism of action is not yet fully understood [1364-1366] (LE: 1b). The main use of terbutaline is for prevention of recurrent episodes of prolonged erection. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema or hypokalaemia [1366]. In a single multi-centre prospective study, another β-2-agonist, salbutamol, has been reported to induce detumescence in 34% of cases of prolonged erection (more than 3 hours) after intracavernous injection of erectogenic agents [1367]. However, more robust data are needed to recommend oral salbutamol for the treatment of ischaemic priapism.

Anti-thrombotic agents
Ramstein *et al.* reported retrospective data pertaining to the use of antithrombotic therapy (a single dose of subcutaneous heparin or aspirin 325 mg) in patients who had undergone corporeal aspiration with and without phenylephrine. Antithrombotic therapy was associated with a significant reduction in further episodes of priapism following aspiration and successful T-shunt insertions in those who failed aspiration. However, these findings were based on a small cohort size (n = 18), doses and types of antithrombotic therapy were heterogeneous, and exact timing of the priapism episodes was not measured precisely. In this setting, further prospective randomised trials are needed prior to the recommendation of antithrombotic agents for treatment or adjunctive therapy in the management of ischaemic priapism [1368].

Table 37: Medical treatment of ischaemic priapism

Drug	Dose/Instructions for use
Phenylephrine	• Intracavernous injection of 200 µg every 3-5 minutes. • Maximum dosage is 1 mg within 1 hour. • Lower doses are recommended in children and patients with severe cardiovascular diseases.
Etilephrine	• Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	• Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis compressed for an additional 5 minutes.
Adrenaline	• Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over a 20-minute period.
Terbutaline	• Oral administration of 5 mg for priapism lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

Management of priapism related to sickle cell disease
The Panel conducted a systematic review on the overall management of priapism related to sickle cell disease. Unfortunately, few studies were conducted exclusively on patients with SCD and studies on mixed populations usually did not report separate data on SCD patients. Clear and systematic reporting of patient characteristics, interventions and outcomes was lacking, and the length of follow-up, if reported, varied significantly among the studies. Overall, the quality of studies was deemed poor for high-quality, evidence-based recommendations.

Urgent intervention is essential (LE: 4) and the general approach is similar to that described for other cases of ischaemic priapism and should be co-ordinated with a haematologist [1355, 1369, 1370] (LE: 4).

However, as with other haematological disorders, other therapeutic interventions may also need to be implemented [1369-1371]. Specific measures for SCD-related priapism include intravenous hydration and narcotic analgesia while preparing the patient for aspiration and irrigation. Additionally, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [1321, 1355].

Haemoglobin S (HbS) percentage should be measured in all SCD patients with acute priapism. Exchange blood transfusion has also been proposed, with the aim of increasing tissue delivery of oxygen [1372]. The transfused blood should be sickle cell haemoglobin negative and Rh and Kell antigen matched [1373]. However, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve priapism. A systematic review reported that the mean time to detumescence was eleven days with exchange transfusions compared to eight days with conventional treatment. Moreover, there were 9 cases of ASPEN syndrome (association of sickle cell disease, priapism, exchange transfusion and neurological events) as a consequence of blood transfusion [1374].

Consensus recommendation: exchange transfusion should not be used as a primary treatment for ischaemic priapism in patients with SCD.
Several reports suggest that exchange transfusion may result in serious neurological sequelae [1374], although a series of 10 patients with SCD-related priapism showed that it was safe to perform exchange transfusion [1372]. Because of these considerations, routine use of exchange transfusion is not recommended as a primary treatment intervention in this group unless there is a risk of SCD-related symptoms (LE: 4). However, in patients who fail medical management, transfusion may be required to enable general anaesthesia to be safely administered prior to definitive surgery [1375].

9.1.3.2 Surgical management

Evidence acquisition
The majority of the identified studies for surgical management were retrospective and non-randomised. A significant proportion of the reports were case series reporting on one or two particular types of surgical procedures, often with low patient numbers (< 20) (Appendix 2). The studies showed a wide variation in data, including the proportion of patients who had prior conservative management, reporting of initial success, and duration of follow-up. Surgical complications were also not consistently reported. The systematic review captured specific end points of priapism resolution, sexual function and surgical adverse events when reported. However, due to the heterogeneity of the data, direct comparisons of success rates and long-term outcomes should be treated with caution.

9.1.3.2.1 Second-line treatments

Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and penile implant insertion for refractory or delayed ischaemic priapism, and should only be considered when other conservative management options fail (LE: 4). There is no evidence detailing the time frames before moving on to surgery after first-line treatment, although a period of at least 1 hour of first-line treatment without detumescence can be considered prior to moving to surgical intervention (LE: 4).

A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis, anoxia, severe glucopenia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressure [1376]. Colour duplex US of the penis in the ischaemic state may be helpful but it should be noted that blood flow may persist in the tumescent phase of erection [1377] (LE: 4).

9.1.3.2.1.1 Penile shunt surgery

Penile shunt surgery aims to produce an outflow for ischaemic blood from the corpus cavernosum thereby allowing restoration of normal circulation within these structures. Accordingly, a shunt creates an opening in the tunica albuginea, with either the glans, corpus spongiosum, or a vein for blood drainage (Table 37) [1304, 1340, 1378].

The type of shunt procedure is chosen according to the surgeon's preference and familiarity with the procedure. It is conventional for distal shunt procedures to be tried before considering proximal shunting (LE: 4). Gadolinium-enhanced penile MRI [1336] and cavernosal smooth muscle biopsy have been used to diagnose smooth muscle necrosis (which, if present, would suggest that shunting is likely to fail) and may help

in decision-making and patient counselling in cases of refractory or delayed presentation (> 48 hours) that may be considered for immediate penile prosthesis insertion (see below).

It is important to assess the success of surgery by direct observation of penile rigidity or by repeated testing (e.g., cavernous blood gas testing) (LE: 4) [1304, 1340, 1379, 1380]. The use of penile colour US may not give appropriate information because of the hyperaemic (reperfusion) period that follows decompression after the ischaemic state [1377].

The recovery rates of erectile function in men undergoing shunt surgery following prolonged episodes of priapism are low and are directly related to the duration of priapism, pre-operative erectile status and age [1379-1381]. The exact duration of priapism for shunt surgery to preserve erectile function is not based on studies with high levels of evidence. If ischaemic priapism resolves within 24 hours of onset, it has been reported that 78-100% of patients regain spontaneous functional erections (with or without PDE5Is use). In contrast, other studies have shown that priapism for more than 36-48 hours appears to result in both structural and functional effects on corporal smooth muscle, with poorer outcomes (ED > 90%) [1379, 1382]. In general, shunt procedures undertaken after this time period (36-48 hours) may only serve to limit pain without any beneficial effects on erectile function and early prosthesis insertion can be considered [1311, 1383].

Four categories of shunt procedures have been reported [1304, 1341, 1378, 1383]. The limited available data preclude any overall recommendation for one procedure over another based upon outcomes, but distal shunts are less invasive and associated with lower rates of post-operative ED and therefore are recommended as the first surgical intervention of choice (Table 37) (LE: 4).

Percutaneous distal (corpora-glanular) shunts
Winter's procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpus cavernosum [1304, 1318, 1341, 1377, 1384] (LE: 3). Post-operative sequelae are uncommon [1385]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [1380]. This is because the diameter of the Trucut needle is only 1.6 mm (14-18 g) and therefore cannot accommodate the increased blood flow from post-ischaemic hyperaemia, resulting in poor drainage, increased intracavernous pressure and consequent premature closure of the shunt [1377].

Ebbehoj's technique involves making multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [1304, 1341, 1377, 1386, 1387] (LE: 3).

T-Shunt involves performing a bilateral procedure using a scalpel with a size 10 blade inserted through the glans just lateral to the urethral meatus until it enters the tip of the corpus cavernosum. The blade is then rotated 90° away (to the lateral side) from the urethral meatus and withdrawn [1304, 1341, 1377, 1388] (LE: 3). If unsuccessful, the procedure is repeated on the opposite side. The T-shunt can be followed by a tunnelling procedure using a size 8/10 Hegar dilator inserted through the glans and into the corpus cavernosum, which can also be performed using US guidance, mainly to avoid urethral injury [1388]. The entry sites in the glans are sutured following detumescence. Tunnelling with a 7 mm metal sound or 7/8 Hegar dilator is necessary in patients with priapism duration > 48 hours. Tunnelling is a potentially attractive procedure as it combines the features of distal and proximal shunts with proximal drainage of the corpus cavernosum and may ameliorate the profibrotic effect of sludged blood retained in the corpus cavernosum [1381, 1383, 1388].

Open distal (corpora-glanular) shunts
Al-Ghorab's procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with subsequent glans closure by running suture with absorbable material. A transverse incision on the glans may compromise arterial blood flow because distal deep dorsal arteries run longitudinally in the glans [1304, 1341, 1377, 1389-1391] (LE: 3).

Burnett's technique (Snake manoeuvre) is a modification of the Al-Ghorab corpora-glanular shunt. It involves retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glanular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis is closed as in the Al-Ghorab procedure [1304, 1341, 1377, 1392, 1393] (LE: 3). Reported complications include wound infection, penile skin necrosis and urethrocutaneous fistulae [1393].

Table 38: Distal shunt procedures in ischaemic priapism

Study	N: (shunt/ shunt + tunnelling)	Duration of priapism (shunt/shunt + tunnelling)	Type of surgery	Detumescence rate (shunt/shunt + tunnelling)	Post-operative ED rate (shunt/shunt + tunnelling)
Ercole *et al.* [1389]	7 (7/0)	2.6 d / NA	Al-Ghorab	100% / NA	57% / NA
Macaluso *et al.* [1385]	12 (12/0)	58 h / NA	Winter	100% / NA	17% / NA
Nixon *et al.* [1380]	14 (14/0)	42 h / NA	Winter	14% / NA	90% / NA
Lund *et al.* [1387]	18 (18/0)	20 h to 8 months / NA	Ebbehoj	61% / NA	39% / NA
Brant *et al.* [1388]	13 (6/7)	50 h / 80 h	T-shunt/T-shunt + tunnelling	46% / 92%	16% / 57%
Segal *et al.* [1393]	10 (0/10)	NA / 60 h	Al-Ghorab + tunnelling	NA / 80%	NA / 40%
Zacharakis *et al.* [1383]	45 (0/45)	NA / 96 h	T-shunt + tunnelling	NA / 64%	NA / 93%
Ortaç *et al.* [1381]	19 (6/13)	48h / 70h	T-shunt/T-shunt + tunnelling	31% / 94%	83% / 85%
Summary	138 (63/75)	52h / 76h		60% / 82%	50% / 68%

ED = erectile dysfunction; h = hours; d = days.

Open proximal (corpora-spongiosal) shunts

Quackles's technique uses a trans-scrotal or perineal approach; a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethro-cavernous fistula and urethral stricture or cavernositis [1304, 1341, 1378, 1394]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum (LE: 3). Proximal shunts are more invasive and ED rates are documented to be higher [1376].

Peno-scrotal decompression

More recently a proximal decompression technique with the aim to spare the glans with high success rates has been described. The technique is based upon opening of the proximal corpus cavernosum combined with proximal and distal tunnelling using a suction tip [1395]. In a cohort of 25 patients, 12 had undergone previous corpora-glanular shunt surgery. Recurrence was observed in two of 25 patients with unilateral peno-scrotal decompression. In the 15 patients who had follow-up data, 40% had ED. Whilst, representing a promising technique, PSD in cases of refractory priapism may further delay penile prosthesis insertion with detrimental effects on surgical outcomes including penile shortening and prosthetic infection.

Anti-thrombotic agents

Procedures for shunting require incision through the tunica albuginea and expose collagen to coagulation factors in the penile blood and thus activate the blood-clotting cascade. Peri-operative anti-coagulation is advocated to facilitate resolution of the priapism. There was an 84% decrease in priapism recurrence in the shunt group that received peri-procedural anti-thrombotic treatment (325 mg acetylsalicylic acid pre-operatively, and 5000 IU intraoperative heparin, post-operatively for 5 days (81 mg acetylsalicylic acid and 75 mg clopidogrel) compared with the group that did not receive peri-procedural anti-thrombotic treatment after failed aspiration [1368].

Vein anastomoses/shunts

Grayhack's procedure mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [1304, 1341, 1396-1398] (LE: 3).

Immediate penile prosthesis implantation

The literature pertaining to penile implantation surgery is shown in Appendix 3. The studies identified here were principally retrospective non-randomised case series. In all but one study, patients had prior non-surgical management. All of the studies described priapism resolution rate, sexual function and surgical adverse events although the follow-up period was variable.

Refractory, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48 hours usually result in complete ED, possibly along with significant penile deformity in the long-term. In these cases, immediate penile prosthesis surgery is advocated [1399-1402] (LE: 3).

The immediate insertion of a malleable penile prosthesis is recommended to avoid the difficulty and complications of delayed prosthetic surgery in the presence of corporal fibrosis. Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and infection [1399, 1401], along with a small rate of revision surgery [1399]. Early surgery also offers the opportunity to maintain penile length and girth and prevent penile curvature due to cavernosal fibrosis. The prosthesis can be exchanged for an inflatable prosthesis at a later date, which may allow upsizing of the implant cylinders [1403].

Currently, there are no clear indications for immediately implanting a penile prosthesis in men with acute ischaemic priapism, although this can be considered in men with delayed or refractory priapism (see below [1340]).

Consensus recommendation [1304] (LE: 4):
Relative indications include:

- Ischaemia that has been present for more than 48 hours;
- Failure of aspiration and sympathomimetic intracavernous injections in delayed priapism (> 48 hours);
- Magnetic resonance imaging or corporal biopsy evidence of corporal smooth muscle necrosis [1304, 1399] (LE: 4);
- Failure of a shunting procedure (although in delayed cases [> 48 hours], implantation might be considered ahead of shunt surgery);
- Refractory priapism in patients who have undergone shunting procedures.

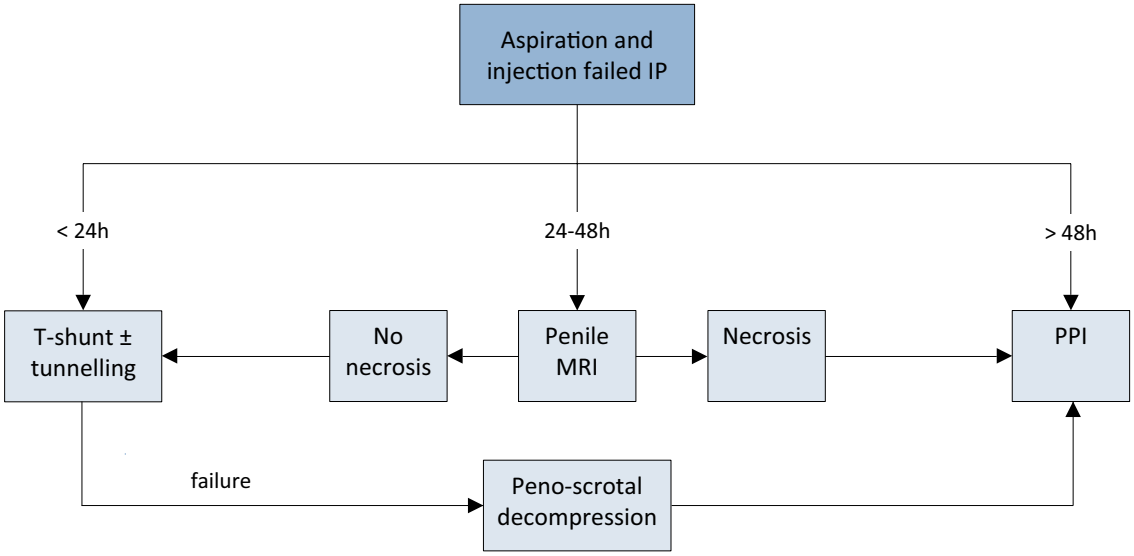
The optimal time for implantation is within the first three weeks from the priapism episode [1311, 1376, 1404]. If shunt surgery has been performed, penile prosthesis implantation can be further delayed in order to allow reduction of oedema, wound healing and risk of prosthetic infection. A vacuum device to avoid fibrosis and penile shortening may be used during this waiting period [1405].

The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience, and availability and cost of the equipment. There are no randomised trials comparing the efficacy and complication rates of malleable and inflatable penile prostheses. Despite the higher infection rate in priapism patients compared to those with virgin prosthesis, in patients who are well-motivated and counselled prior to the procedure, immediate inflatable penile prosthesis implantation may be undertaken, although in most cases a semi-rigid implant is more suitable as it is easier to implant and reduces operative time and hence the risk of prosthetic infection. A further issue with immediate insertion of an inflatable penile prosthesis is that the patient must begin cycling the device immediately to avoid a fibrous capsule forming and contracting. Early cycling of an inflatable penile prosthesis prevents penile curvature and shortening [1311].

Surgery for non-acute sequelae after ischaemic priapism
Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss [1378, 1399, 1406, 1407]. Erectile dysfunction is also often observed [1304, 1408]. Unfortunately, these outcomes can still occur despite apparently successful first-line or second-line treatment in detumescence of the penis.

Penile prosthesis implantation is occasionally indicated in SCD patients with severe ED because other therapeutic options, such as PDE5Is and intracavernous injections are avoided as they may provoke a further priapism event [1304, 1340]. In severe corporal fibrosis, narrow-based prosthetic devices are preferable because they are easier to insert and need less dilatation [1399] (LE: 3). After severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, it may be necessary to make changes to the surgical technique. Multiple corporotomies, corporal excavation, optical corporotomy-Shaeer technique, dilatation with Carrion-Rosello cavernotome, Uramix or Mooreville cavernotome, excision of scar tissue, and use of small-diameter prosthesis, or penile reconstruction using grafts can be utilised, if concomitant prosthesis implantation is considered [1382, 1409] (LE: 3). Early implantation of a penile prosthesis is associated with lower infection rates (6-7% vs. 19-30%), penile shortening (3% vs. 40%) and revision rates (9% vs. 27%) compared to late insertion. General satisfaction rate for early implantation is higher (96%) than for late implantation (60%) [1311] (Appendix 4).

Figure 14: Algorithm on surgical management of priapism



IP = ischaemic priapism; MRI = Magnetic resonance imaging; PPI = penile prosthesis implantation.

9.1.4 Summary of evidence for treatment of ischaemic priapism

Summary of evidence	LE
Emergency intervention for ischaemic priapism is mandatory.	2b
The aim of treatment aim is to facilitate painless penile detumescence, to prevent chronic fibrosis of the corpus cavernosum.	3
Erectile function preservation is directly related to the duration of ischaemic priapism, age and pre-operative erectile status.	2b
Phenylephrine is the recommended drug due to its favourable safety profile in the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour. Patients at high cardiovascular risk should be given lower doses. Patient monitoring is highly recommended.	2b
Gadolinium-enhanced MRI may be useful to diagnose smooth muscle necrosis in cases of delayed or refractory priapism.	3
Shunt procedures are effective to resolve priapism and provide pain relief. No clear recommendation of the superiority of one type of shunt over another can be given. Distal shunts are less invasive and associated with lower rate of erectile dysfunction.	2b
Peri- and post-operative anticoagulant prophylaxis (325 mg acetylsalicylic acid pre-operatively, 5,000 IU heparin intra-operatively and 81 mg acetylsalicylic acid and 75 mg clopidogrel five days post-operatively) may prevent priapism recurrence.	3
Erectile dysfunction is almost inevitable in prolonged cases or ischaemic priapism. Early implantation of penile prosthesis is associated with lower infection rates and complications compared to late implantation.	2b

9.1.5 Recommendations for the treatment of ischaemic priapism

Recommendations	Strength rating
Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach.	Strong
First, decompress the corpus cavernosum by penile aspiration and washout until fresh red blood is obtained.	Strong
In priapism secondary to intracavernous injections of vasoactive agents, replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step.	Strong
In priapism that persists despite aspiration, proceed to the next step, which is intracavernous injection of a sympathomimetic drug.	Strong

In cases that persist despite aspiration and intracavernous injection of a sympathomimetic drug, repeat these steps before considering surgical intervention.	Strong
Treat ischaemic priapism associated with sickle cell disease in the same fashion as idiopathic ischaemic priapism. Provide other supportive measures (intravenous hydration, oxygen administration with alkalisation with bicarbonate, blood exchange transfusions), but do not delay initial treatment to the penis.	Strong
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed.	Strong
Perform distal shunt surgical procedures first and combine them with tunnelling if necessary.	Weak
Proximal procedures may be used in cases of distal shunt failure (< 48 hours) or in patients who do not wish to proceed with immediate penile implant insertion.	Weak
Peri- and post-operative anticoagulation may decrease priapism recurrence.	Weak
A penile prosthesis may be preferred over proximal shunting particularly in delayed (> 48 hours) or refractory priapism	Weak
Implantation of a prosthesis may be considered in delayed presentation (> 48 hours) and in those cases refractory to injection therapy and distal shunting.	Weak
If a shunt has been performed, then implantation of a penile prosthesis should be delayed to minimise the risk of infection and erosion of the implant.	Strong
The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience and availability and cost of the equipment. If malleable penile prosthesis is implanted it can be later exchanged to an ınflatable penıle implant.	Strong
Patients must be fully counselled regarding the risks and benefits of implant insertion in every case of delayed presentation of refractory priapism.	Weak

9.2 Priapism in Special Situations

*9.2.1 **Stuttering (recurrent or intermittent) priapism***

9.2.1.1 Epidemiology/aetiology/pathophysiology

Robust epidemiological studies of stuttering priapism are lacking [1410, 1411]. However, recurrent priapism episodes are common in men with SCD (42-64%) [1412, 1413] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [1410].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. Whilst SCD is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Men who have acute ischaemic priapism, especially which has been prolonged (for more than 4 hours) are at risk of developing stuttering priapism [1408].

Several studies have proposed alternative mechanisms for stuttering priapism including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation [1304, 1322, 1355, 1414, 1415]. Specifically, a deficiency in endothelial NO causes downregulation in a cyclic guanosine monophosphate (cGMP)-dependent protein kinase and PDE5, resulting in dysregulation in the corporal smooth muscle tone [1416]. Furthermore, decreased NO availability decreases RhoA (Ras homolog gene family) and Rho-kinase, which are important factors for penile detumescence, and disrupts adenosine signalling [1417]. The lack of mechanisms to regulate cGMP, along with reduced vasoconstriction, reduce cavernosal smooth muscle tone, leading to an increased and disproportionate response to stimuli. Adenosine, like NO, is a potent vasodilator and regulator of penile tumescence. It is increased in conditions of stress, hypoxia and ischaemia, suggesting an important role in the pathogenesis of the priapic state [1418]. Finally, although debated, androgens have also been observed to have an association with priapism [1419]. Androgens play an important role in the mediation of erections both centrally and peripherally. They are known to contribute toward the regulatory basis of both NO synthase and PDE5 expression and activity in various structures of the local erectile apparatus [1420]. Therefore, one of the options for the treatment of stuttering priapism is to reduce serum testosterone levels to hypogonadal levels, which then suppresses androgen-associated mechanisms believed to be involved in triggering recurrent priapism.

9.2.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of stuttering priapism

Summary of evidence	LE
Stuttering priapism is similar to ischaemic priapism in that it is low-flow and ischaemic and, if left untreated, can result in significant penile fibrosis, with SCD being the most common cause.	3

9.2.1.2 Classification

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limiting with intervening periods of detumescence [1355, 1414]. These are analogous to repeated episodes of ischaemic priapism. In stuttering priapism the duration of the erections is generally shorter than in ischaemic priapism [1341]. The frequency and/or duration of these episodes is variable and a single episode can sometimes progress into prolonged ischaemic priapism.

9.2.1.3 Diagnostic evaluation

9.2.1.3.1 History

A comprehensive history is mandatory and follows the same principles as described in Table 33. There is a history of recurrent episodes of prolonged erections. These episodes can occur from several daily to isolated incidents every few months, continuously or followed by incident-free periods, of unknown duration, even months and years [1421]. The onset of the priapic episodes usually occurs during sleep and detumescence does not occur upon waking. These episodes can be painful and may be the reason that the patient first seeks medical attention. Priapism can cause significant impairment of mental health with patients experiencing sadness, embarrassment, fear, and exhaustion [1422].

9.2.1.3.2 Physical examination

Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalo-phallus.

9.2.1.3.3 Laboratory testing

Laboratory testing follows the same principles as in the two other types of priapism. It is recommended to identify possible causes and should be directed by the history and clinical and laboratory findings.

9.2.1.3.4 Penile imaging

There are no specific findings on imaging for stuttering priapism. Colour duplex US of the penis and perineum and MRI are recommended and can differentiate non-ischaemic from ischaemic forms of priapism.

9.2.1.3.5 Recommendations for diagnosis of stuttering priapism

The same recommendations as described in Section 9.1.2.5 apply. Stuttering priapism is a recurrent or intermittent type of ischaemic priapism.

9.2.1.4 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of further episodes and limiting the chances of developing a prolonged ischaemic priapism that is refractory to conventional treatment options. In most cases, stuttering priapism can be managed by pharmacological treatment, the aim of which is to reduce the frequency and severity of stuttering episodes. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of α-adrenergic agonists. Unfortunately, the efficacy and safety of the various treatment modalities suggested over the medical literature are poorly reported. Specifically, most reports are from small case series and the Panel is not aware of any published, well-designed, controlled studies on the efficacy and safety of these treatments [1321, 1355, 1414, 1421].

9.2.1.4.1 α-Adrenergic agonists

Studies of oral α-adrenergic agonists have suggested some prophylactic benefit for daily treatment with these agents [1423]. Adverse effects include tachycardia and palpitations. Pseudoephedrine is widely used as an oral decongestant and can be a first-line treatment option for stuttering priapism [1365]. However, its effect on corporal smooth muscle is not fully understood. Etilephrine has been used successfully to prevent stuttering priapism caused by SCD. It is usually taken orally at doses of 5-10 mg daily, with response rates of up to 72% [1424-1426]. In one randomised, placebo-controlled clinical study comparing medical prophylaxis with etilephrine and ephedrine, there was no difference in efficacy between the two drugs.

9.2.1.4.2 Hormonal manipulations of circulating testosterone

The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [1321, 1355, 1427]. This can be achieved by GnRH agonists or antagonists, antiandrogens or oestrogens [1428, 1429] (LE: 4). Potential adverse effects may include hot flushes, gynaecomastia, ED, loss of libido, and asthenia. All approaches have a similar efficacy profile (LE: 4) while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5-α-reductase inhibitors [1430, 1431] (LE: 3) and ketoconazole; an anti-fungal agent that reduces adrenal and testicular androgen production [1427, 1432] (LE: 4).

The duration of hormonal treatment for effective suppression of recurrent priapism is problematic. It is not possible to draw any conclusions on the dose, duration of treatment and the efficacy. Caution is strongly advised when prescribing hormonal treatments to pre-pubertal boys and adolescents, and specialist advice from paediatric endocrinologists should be sought. Likewise, hormonal agents have a contraceptive effect and interfere with normal sexual maturation and spermatogenesis and affect fertility. Therefore, men who are trying with their partner to conceive should be comprehensively counselled before using hormonal treatment. Moreover, sperm cryopreservation may be considered to mitigate any potential effects of anti-androgen therapy on fertility.

9.2.1.4.3 Digoxin

Digoxin is a cardiac glycoside and positive inotrope that is used to treat congestive heart failure. Digoxin regulates smooth muscle tone through several different pathways leading to penile detumescence [1321, 1355, 1433]. The use of maintenance digoxin doses (0.25-0.5 mg/daily) in idiopathic stuttering priapism reduces the number of hospital visits and improves QoL [1355]. In a small, clinical, double-blind, placebo-controlled study, digoxin decreased sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and LH [1433] (LE: 2b). Adverse effects include decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

9.2.1.4.4 Terbutaline

Terbutaline is a β-agonist that causes vasodilation, resulting in vascular smooth muscle relaxation [1321, 1355] and has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [1365] (LE: 3). The only randomised, placebo-controlled study (n = 68) in patients with pharmacologically-induced priapism, demonstrated detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [1366] (LE: 1b). Adverse effects include nervousness, shakiness, drowsiness, palpitations, headache, dizziness, hot flushes, nausea and weakness.

9.2.1.4.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and anti-epileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [1427], and reduces testosterone and FSH levels [1434]. It is given at a dose of 400 mg, four times daily, up to 2,400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of 300 mg/daily [1435] (LE: 4). Adverse effects include anorgasmia and impaired erectile function.

9.2.1.4.6 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogenic erections or prolonged erections from neurological diseases [1321]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal administration is more effective [1355, 1436-1438] (LE: 4). Adverse effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

9.2.1.4.7 Hydroxyurea

Hydroxyurea blocks the synthesis of deoxyribonucleic acid (DNA) by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [1427, 1439]. Hydroxyurea is an established treatment for ameliorating SCD and improving life expectancy [1369, 1440]. For patients with recurrent priapism, there is limited evidence to suggest a prophylactic role of hydroxyurea (LE: 3), [1427, 1439, 1441]. Adverse effects include oligo-zoospermia and leg ulcers.

9.2.1.4.8 Phosphodiesterase type 5 inhibitors

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism; mainly in patients with idiopathic and SCD-associated priapism [1321, 1355, 1416, 1442-1446] (LE: 3). It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function (LE: 3). Phosphodiesterase type 5 inhibitor treatment of stuttering priapism is possibly mediated by an increase in the concentration of cGMP in the smooth muscle in an NO dysfunctional state. This can occur in priapism and may result in a change in the NO pathway, with down-regulation of cavernosal PDE5 thereby preventing the complete degradation of cGMP in the corpus cavernosum [1321, 1355, 1416, 1442].

9.2.1.4.9 Intracavernosal injections

Some patients with stuttering priapism, who have been started on systemic treatment to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and temporarily require intracavernous self-injections at home with sympathomimetic agents [1321, 1355]. The most commonly used drugs are phenylephrine and etilephrine (as described in the treatment of ischaemic priapism) [1304, 1341, 1411, 1425] (LE: 3). Adverse effects include hypertension, coronary ischaemia and cardiac arrhythmias.

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the pro-enzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernous injection of TPA can successfully treat patients with recalcitrant priapism [1427, 1447] (LE: 3). Mild bleeding is the most commonly observed adverse effect.

9.2.1.4.10 Penile prosthesis

Patients with medically refractory stuttering priapism require frequent visits to the emergency department and are always at risk of a major ischaemic episode, which can be mitigated with insertion of a penile prosthesis [1382, 1402, 1448]. Nevertheless, penile prosthesis for preventing stuttering priapism should not be offered before medical treatment and a penile prosthesis should be performed only in carefully selected patients as a last resort [1382]. In patients with permanent ED due to stuttering priapism, medical treatments for ED (PDE5Is or intracavernosal injection) should be used cautiously because of the risk of inducing an ischaemic episode and a penile prosthesis can be considered [1382, 1449].

9.2.1.5 Summary of evidence for treatment of stuttering priapism

Summary of evidence	**LE**
The primary goal in the management of patients with stuttering priapism is prevention of future episodes, which can generally be achieved pharmacologically.	2b
Phosphodiesterase type 5 inhibitors have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism.	3
The evidence with other systemic drugs (digoxin, α-adrenergic agonists, baclofen, gabapentin and terbutaline, hydroxyurea) is limited.	3

9.2.1.6 Recommendations for treatment of stuttering priapism

Recommendations	**Strength rating**
Manage each acute episode similar to that for ischaemic priapism.	Strong
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or anti-androgens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	Weak
Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state.	Weak
Use digoxin, α-adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with frequent and uncontrolled relapses.	Weak
Use intracavernous self-injections of sympathomimetic drugs at home for treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	Weak

9.2.1.7 Follow-up

Follow-up for stuttering priapism includes history and clinical examination to assess the efficacy of treatment in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

*9.2.2 **Priapism in children***

The classification of priapism in children is similar to that in adults. In addition to ischaemic, stuttering and non-ischaemic priapism, a fourth type, neonatal priapism is also described [1304]. Priapism in children is considered rare as no data on its prevalence exist. Sickle cell disease is the major cause of priapism in children, followed by leukaemia (10%), trauma (10%), idiopathic causes (19%) and drugs (5%) [1450]. One study showed that 25% of children experienced SCD-related priapism in a pre-pubertal period [1451]. Another study revealed that 90% of men with SCD had their first priapism episode before age 20 years [1413]. Priapism in children should be evaluated and treated in a timely manner, as untreated ischaemic priapism may lead to ED and psychosexual disorders in adulthood [1452]. A multi-disciplinary team approach should be utilised with specialist input from haematologists and paediatric endocrinologists.

9.3 Non-ischaemic (high-flow or arterial) priapism

Most of the identified studies were small retrospective case series reporting principally on the role of embolisation in post-traumatic non-ischaemic priapism (Appendix 5). This may reflect the uncommon nature of the condition. Success rates and erectile function were well documented across all reports. Some studies attempted to stratify outcomes based on the agent used for embolisation (e.g., microcoil or autologous clot), although care should be taken when interpreting case series with small patient numbers.

*9.3.1 **Epidemiology/aetiology/pathophysiology***

Epidemiological data on non-ischaemic priapism are almost exclusively derived from small case series [1304, 1335, 1337, 1453, 1454]. Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases [1304]. The most frequent cause of non-ischaemic priapism is blunt perineal or penile trauma [1455]. The injury results in a laceration in the cavernosal artery or branches, leading to a fistula between the artery and the lacunar spaces of the sinusoidal space [1454]. The resultant increased blood flow results in a persistent and prolonged erection [1456].

There is often a delay between the trauma and the development of the priapism that may be up to two to three weeks [1457]. This is suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment “blows up”. The priapism typically occurs after a nocturnal erection or an erection related to sexual activity, resulting in the sudden increase of blood flow and pressure in the cavernous arteries [1458]. The patient typically reports an erection that is not fully rigid and is not associated with pain because the venous drainage is not compromised and the penile tissue does not become ischaemic [1459].

Non-ischaemic priapism can occur after acute spinal cord injury, presumably due to loss of sympathetic input, leading to predominant parasympathetic input and increased arterial flow [1460]. It has also been reported to occur following internal urethrotomy [1461], Nesbit procedure [1462], circumcision [1463], transrectal prostate biopsy [1464], and brachytherapy for prostate cancer [1465]. Some cases have also been described following shunting procedures performed for ischaemic priapism due to a lacerated cavernosal artery (conversion of low-flow to high-flow priapism) [1466-1468]. Although SCD is usually associated with ischaemic priapism, occasional cases of high-flow priapism have been reported; however, the pathophysiological mechanism remains unclear [1469]. Finally, metastatic malignancy to the penis can also rarely cause non-ischaemic priapism [1470, 1471] (Table 38).

Table 39: Causes of arterial priapism

Perineal or penile trauma
Spinal cord injury
Iatrogenic causes (e.g., shunting procedure for ischaemic priapism)
Sickle cell disease
Metastatic malignancy to the penis
Idiopathic

9.3.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of arterial priapism

Summary of evidence	**LE**
Non-ischaemic priapism is significantly less common than ischaemic priapism.	2b
Non-ischaemic priapism usually occurs after blunt perineal or penile trauma.	2
Non-ischaemic priapism if not treated may cause erectile dysfunction with time.	3

9.3.2 *Classification*

Non-ischaemic priapism is a persistent erection caused by unregulated cavernous arterial inflow [1304]. According to aetiology, non-ischaemic priapism can be categorised into four types: traumatic, neurogenic, iatrogenic and idiopathic in origin.

9.3.3 *Diagnostic evaluation*

9.3.3.1 *History*

A comprehensive history is mandatory in non-ischaemic priapism diagnosis and follows the same principles as described in Table 33. Arterial priapism should be suspected when the patient reports a history of pelvic, perineal, or genital trauma; no penile pain (discomfort is possible); and a persistent, not fully rigid erection (Table 34). The corpus cavernosum can become fully rigid with sexual stimulation, so the sexual intercourse is usually not compromised. The onset of post-traumatic non-ischaemic priapism can be delayed by several hours to weeks following the initial injury [1304].

9.3.3.2 *Physical examination*

In non-ischaemic priapism, the corpora are tumescent but not fully rigid. Abdominal, penile and perineal examination may reveal evidence of trauma (Table 34) [1304]. Neurological examination is indicated if a neurogenic aetiology is suspected.

9.3.3.3 *Laboratory testing*

Laboratory testing should include a blood count with white blood cell differential and a coagulation profile to assess for anaemia and other haematological abnormalities. Blood aspiration from the corpus cavernosum shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism (Table 34) (LE: 2b). Blood gas analysis is essential to differentiate between non-ischaemic and ischaemic priapism. Blood gas values in high-flow priapism show normal arterial blood [1304] (Table 35).

9.3.3.4 *Penile imaging*

Colour duplex US of the penis and perineum is recommended and can differentiate non-ischaemic from ischaemic priapism [1333-1335]. Ultrasound must be performed without intracavernosal vasoactive drug injection [1472]. In non-ischaemic priapism, US helps to localise the fistula site and appears as a characteristic colour blush and turbulent high-velocity flow on Doppler analysis [1473]. Patients with non-ischaemic priapism have normal to high blood velocities in the cavernous arteries [1306, 1474].

Selective pudendal arteriography can reveal a characteristic blush at the site of injury in arterial priapism [1475, 1476]. However, due to its invasiveness, it should be reserved for the management of non-ischaemic priapism when embolisation is being considered [1304, 1329].

The role of MRI in the diagnostic evaluation of priapism is controversial. Its role in non-ischaemic priapism is limited because the small penile vessels and fistulae cannot be easily demonstrated [1477].

9.3.3.5 *Recommendations for the diagnosis of non-ischaemic priapism*

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis, which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a neurological examination if neurogenic non-ischaemic priapism is suspected.	Strong
For laboratory testing, include complete blood count, with white blood cell differential, and coagulation profile.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform selected pudendal arteriography when embolisation is planned for non-ischaemic priapism.	Strong

9.3.4 ***Disease management***

Although the conventional belief is that the management of non-ischaemic priapism is not an emergency because the corpus cavernosum does not contain ischaemic blood, recent data indicate that the duration of non-ischaemic priapism can also effect erectile function. High-flow priapism was reproduced in an in vitro model using pre-contracted strips of rabbit corpus cavernosum superfused at high pO_2 levels. This showed that the smooth muscle tone reduced by 43% after super-fusion for twelve hours, indicating irreversible smooth muscle dysfunction [1478]. In a case series consisting of six patients with high-flow priapism after median follow-up of 4.5 (2-12) weeks, all patients reported development of ED or distal penile flaccidity [1403]. The goal of treatment is closure of the fistula. Non-ischaemic priapism can be managed conservatively or by direct perineal compression. Failure of conservative treatment requires selective arterial embolisation [1479]. The optimal time interval between conservative treatment and arterial embolisation is still under debate. Definitive management can be performed at the discretion of the treating physician and should be discussed with the patients so that they can understand the risks of treatment [1304, 1329].

9.3.4.1 *Conservative management*

Conservative management may include applying ice to the perineum or perineal compression, which is typically US-guided. The fistula occasionally closes spontaneously. Even in those cases where the fistula remains patent, intercourse is still possible [1335, 1453, 1480, 1481]. Androgen deprivation therapy (e.g., leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [1482]. However, sexual dysfunction due to these treatments must be considered. Patients may develop ED or distal penile flaccidity while undergoing conservative treatment [1403].

Blood aspiration is not helpful for the treatment of arterial priapism and the use of α-adrenergic antagonists is not recommended because of potential severe adverse effects (e.g., such as transfer of the drug into the systemic circulation).

9.3.4.2 *Selective arterial embolisation*

Selective arterial embolisation can be performed using temporary substances, such as autologous blood clot [1483-1485] and gel foam [1484, 1486], or permanent substances such as microcoils [1484, 1486-1488], ethylene-vinyl alcohol copolymer (PVA), and N-butyl-cyanoacrylate (NBCA) [1489]. It is assumed that temporary embolisation provides a decreased risk of ED, with the disadvantage of higher failure/recurrence rates; this would be the consequence of artery recanalisation using temporary materials. However, there is insufficient evidence to support this hypothesis. A recent non-systematic review of the literature reported success rates ranging between 61.7 and 83.3%, and ED rates from 0-33.3% after the first arterial embolisation, showing that failure/recurrence may not be significantly higher with temporary embolisation materials, and preservation of erectile function may not be that different between the two modalities either [1458]. Other potential complications of arterial embolisation include penile gangrene, gluteal ischaemia, cavernositis, and perineal abscess [1304, 1490]. Repeated embolisation is a reasonable option for treating non-ischaemic priapism, both in terms of efficacy and safety [1458].

9.3.4.3 *Surgical management*

Surgical ligation of the fistula is possible through a transcorporeal or inguinoscrotal approach, using intra-operative Doppler US. Surgery is technically challenging and associated with significant risks, particularly of ED [1491]. Surgery is rarely performed and should only be considered when there are contraindications for selective embolisation, if embolisation is unavailable, or repeated embolisations have failed. If the patient desires more definitive treatment and is not sexually active or has pre-existing ED, surgical intervention can be an appropriate option [1458]. Erectile dysfunction rates ranging from 0-50% are reported following non-ischaemic priapism and its treatment, with surgical ligation having the highest reported rates [1458]. Patients can require penile prosthesis implantation for ED in the long-term [1382].

9.3.4.4 *Summary of evidence for the treatment of arterial priapism*

Summary of evidence	**LE**
Non-ischaemic priapism can cause erectile dysfunction over time and early definitive management should be undertaken.	3
Conservative management applying ice to the perineum or site-specific perineal compression is an option in all cases. The use of androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	3

Selective artery embolisation, using temporary or permanent substances, has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation and success rate.	3
Repeated embolisation is a reasonable option for the treatment of non-ischaemic priapism.	2b
Selective surgical ligation of the fistula should be reserved as the last treatment option when multiple embolisations have failed.	3

9.3.4.5 Recommendations for the treatment of arterial priapism

Recommendations	Strength rating
As non-ischaemic priapism is not an emergency, perform definitive management at the discretion of the treating physician.	Weak
Manage conservatively with the use of site-specific perineal compression as the first step. Consider androgen deprivation therapy only in adults.	Weak
Perform selective arterial embolisation when conservative management has failed.	Strong
Perform first selective arterial embolisation using temporary material.	Weak
Repeat the procedure with temporary or permanent material for recurrent non-ischaemic priapism following selective arterial embolisation.	Weak
Reserve selective surgical ligation of a fistula as a final treatment option when repeated arterial embolisations have failed.	Weak

9.3.4.6 High-flow priapism in children

Non-ischaemic priapism is a rare condition, especially in children. The embarrassment that children may have in speaking about it to their parents can lead to misdiagnosis and underestimating the prevalence of this condition [1492]. The aetiology, clinical presentation and diagnostic and therapeutic principles are comparable with those of arterial priapism in adults. However, some differentiating features should be noted.

Idiopathic non-ischaemic priapism can be found in a significant percentage of children [1493]. Perineal compression with the thumb may be a useful manoeuvre to distinguish ischaemic and non-ischaemic priapism, particularly in children, where it may result in immediate detumescence, followed by the return of the erection with the removal of compression [1458]. Conservative management using ice applied to the perineum or site-specific perineal compression may be successful, particularly in children [1494, 1495]. Although reportedly successful, embolisation in children is technically challenging and requires treatment within a specialist paediatric vascular radiology department [1345, 1496].

9.3.4.7 Follow-up

During conservative management of non-ischaemic priapism, physical examination and colour duplex US can be useful tools to assess treatment efficacy. Close follow-up using colour duplex US and MRI can help detect distal penile fibrosis and be beneficial in clinical decision-making to intervene with embolisation earlier [1403]. Follow-up after selective arterial embolisation should include clinical examination, colour duplex US, and erectile function assessment. If in doubt, repeat arteriography is required. The goals are to determine if the treatment was successful, identify signs of recurrence, and verify any anatomical and functional sequelae [1472].

9.4 Controversies and future areas of focus in the management of priapism

Low-flow priapism should be considered as a surgical emergency. Although the treatment of high-flow priapism can be delayed, there is some evidence to suggest that a delay in intervention may result in long-term fibrosis of the corpus cavernosum.

The evidence in the literature mainly consists of retrospective single centre cohort studies and therefore is of low quality. Prospective multicentre studies are needed to develop high levels of evidence to support contemporary guidelines.

There are a number of controversial areas including the prophylaxis of stuttering priapism, with no real evidence suggesting the superiority of a single pharmaceutical agent over another. In particular, understanding of the time point at which irreversible corporal smooth muscle necrosis occurs due to low-flow priapism is limited; therefore, definitive management of delayed or refractory priapism remains controversial (i.e., immediate prosthesis implantation vs. penoscrotal decompression vs. shunting). Therefore, it is strongly recommended that multi-centre collaborative studies are performed to better understand this rare but devastating condition.

10. MALE INFERTILITY

10.1 Definition and classification

Infertility is defined by the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy within 1 year [1497]. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least 12 consecutive months having sex without using birth control methods. Secondary infertility refers to infertile couples who have been able to achieve pregnancy at least once before (with the same or different sexual partner). Recurrent pregnancy loss is distinct from infertility and is defined as two or more failed pregnancies [1498, 1499].

10.2 Epidemiology/aetiology/pathophysiology/risk factors

*10.2.1 **Introduction***

About 15% of couples do not achieve pregnancy within 1 year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child [1500]. In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters [1497]. For this reason, all male patients belonging to infertile couples should undergo medical evaluation by a urologist trained in male reproduction.

Male fertility can be impaired as a result of [1497]:

- congenital or acquired urogenital abnormalities;
- gonadotoxic exposure (e.g., radiotherapy or chemotherapy);
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g., as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male-associated factor is found to explain impairment of sperm parameters and historically was referred to as idiopathic male infertility. These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine, genetic and biochemical laboratory testing, although semen analysis may reveal pathological findings (see Section 10.3.2). Unexplained male infertility is defined as infertility of unknown origin with normal sperm parameters and partner evaluation. Between 20 and 30% of couples will have unexplained infertility. It is now believed that idiopathic male infertility may be associated with several previously unidentified pathological factors, which include but are not limited to endocrine disruption as a result of environmental pollution, generation of reactive oxygen species (ROS)/sperm DNA damage, or genetic and epigenetic abnormalities [1501].

Advanced paternal age has emerged as one of the main risk factors associated with the progressive increase in the prevalence of male factor infertility [1502-1509]. Likewise, advanced maternal age must be considered over the management of every infertile couple, and the consequent decisions in the diagnostic and therapeutic strategy of the male partner [1510, 1511]. This should include the age and ovarian reserve of the female partner, since these parameters might determine decision-making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology [ART] vs. surgical intervention) [1502-1505]. Table 40 summarises the main male-infertility-associated factors.

Table 40: Male infertility causes and associated factors and percentage of distribution in 10,469 patients [1512]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
Infertility of known (possible) cause	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm auto-antibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	< 0.1	0.3
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
Others	0.8	0.8
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
Disturbance of erection/ejaculation	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (congenital bilateral absence of vas deferens)	0.5	3.0
Others	0.8	1.9

CBAVD = Congenital bilateral absence of the vas deferens.

10.2.2 ***Recommendations on epidemiology and aetiology***

Recommendations	Strength rating
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Infertility should be evaluated after 6 months of attempted conception when the female partner is aged > 35 years.	Weak
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters for urogenital abnormalities.	Strong

10.3 Diagnostic work-up

Focused evaluation of male patients must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [1513], and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and semen parameters.

10.3.1 ***Medical/reproductive history and physical examination***

10.3.1.1 Medical and reproductive history

Medical history should evaluate any risk factors and behavioural patterns that could affect the male partner's

fertility, such as lifestyle, family history (including, testicular cancer), comorbidity (including systemic diseases; e.g., hypertension, diabetes mellitus, obesity, MetS, testicular cancer, etc.), genito-urinary infections (including sexually transmitted infections), history of testicular surgery and exclude any potential known gonadotoxins [1514].

Typical findings from the history of a patient with infertility include:
- cryptorchidism (uni- or bilateral);
- testicular torsion and trauma;
- genitourinary infections;
- exposure to environmental toxins;
- gonadotoxic medications (anabolic drugs, chemotherapeutic agents, etc.);
- exposure to radiation or cytotoxic agents.

10.3.1.2 Physical examination

Focused physical examination is compulsory in the evaluation of every infertile male, including presence of secondary sexual characteristics. The size, texture and consistency of the testes must be evaluated. In clinical practice, testicular volume is assessed by Prader's orchidometer [1515]; orchidometry may over-estimate testicular volume when compared with US assessment [1516]. There are no uniform reference values in terms of Prader's orchidometer-derived testicular volume, due to differences in the populations studied (e.g., geographic area, nourishment, ethnicity and environmental factors) [1515-1517]. The mean Prader's orchidometer-derived testis volume reported in the European general population is 20.0 ± 5.0 mL [1515], whereas in infertile patients it is 18.0 ± 5.0 mL [1515, 1518, 1519]. The presence of the vas deferens, fullness of epididymis and presence of a varicocele should be always determined. Likewise, palpable abnormalities of the testis, epididymis, and vas deferens should be evaluated. Other physical alterations, such as abnormalities of the penis (e.g., phimosis, short frenulum, fibrotic nodules, epispadias, hypospadias, etc.), abnormal body hair distribution and gynecomastia, should also be evaluated.

Typical findings from the physical examination of a patient with characteristics suggestive for testicular deficiency include:
- abnormal secondary sexual characteristics;
- abnormal testicular volume and/or consistency;
- testicular masses (potentially suggestive of cancer);
- absence of testes (uni-bilaterally);
- gynaecomastia;
- varicocele.

10.3.2 ***Semen analysis***

A comprehensive andrological examination is always indicated in every infertile couple, both if semen analysis shows abnormalities, and even in the case of normal sperm parameters as compared with reference values [1520]. Important treatment decisions are based on the results of semen analysis and most studies evaluate semen parameters as a surrogate outcome for male fertility. However, semen analysis cannot precisely distinguish fertile from infertile men [1521]; therefore, it is essential that the complete laboratory work-up is standardised according to reference values (Table 41). There is consensus that modern semen analysis must follow these guidelines. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the most updated version of the WHO Laboratory Manual for the Examination and Processing of Human Semen. Of note, the 6th edition the WHO Manual for the Examination and Processing of Human Semen [1522] has been published on July 2021 and reports some differences compared to the previous edition (5th edn.) [1523] that has been used throughout the last eleven years. Therefore, it is possible that the worldwide implementation in the everyday clinical practice of the newly-released version could be gradual.

The 6th edn. of the WHO Manual is more like a technical guideline rather than a clinical guideline. Accordingly, it comprises three sections: i) semen examination; ii) sperm preparation and cryopreservation; and, iii) quality assessment and quality control.

Overall, the procedures for semen examination are divided into three chapters:
- Basic examinations, which contains fewer investigations than the previous edition that should be performed by every laboratory, based on step-wise procedures and evidence based techniques.
- Extended analyses, which are performed by choice of the laboratory or by special request from the clinicians.
- Advanced examinations, that are classified as focused on very specialized as well as mainly research methods and other emerging technologies.

Overall, a few relevant differences have been identified between 6th and 5th editions.

Basic examination:

- Assessment of sperm numbers: the laboratory should not stop assessing the number of sperm at low concentrations (2 million/mL), as suggested in the 5th edition, but report lower concentrations, noting that the errors associated with counting a small number of spermatozoa may be very high. In this edition, it is recognised that the total sperm numbers per ejaculate (sperm output) have more diagnostic value than sperm concentration; therefore, semen volume must be measured accurately.
- Assessment of sperm motility: the categorisation of sperm motility has reverted back to fast progressively motile, slow progressively motile, non-progressively motile and immotile (grade a, b, c or d) because presence (or absence) of rapid progressive spermatozoa is recognised to be clinically important.
- Assessment of sperm morphology: the 6th edition has recommended the Tygerberg strict criteria by sperm adapted Papanicolaou staining.

Moreover, vitality test should not be performed in all samples and only if few motile sperm are found.

Extended examinations

This chapter contains procedures to detect leukocytes and markers of genital tract inflammation, sperm antibodies, indices of multiple sperm defects, sequence of ejaculation, methods to detect sperm aneuploidy, semen biochemistry and sperm DNA fragmentation.

Advanced examinations

Obsolete tests such as the human oocyte and human zona pellucida binding and the hamster oocyte penetration tests have been completely removed. Research tests include assessment of ROS and oxidative stress, membrane ion channels, acrosome reaction and sperm chromatin structure and stability, computer-assisted sperm analysis (CASA).

Reference ranges and reference limits

In the 5th edition, the distribution of values from approximately 1,800 men who have contributed to a natural conception within 12 months of trying was presented and the lower fifth percentile of this distribution has been considered as a true cutoff limit for normal vs. abnormal sperm parameters [1513].

The 6th edn highlights that distribution of data from reference men do not represent limits between fertile and subfertile individuals [1522]. Indeed, in the latest edition of the WHO Manual, the data presented in the 5th edition have been further evaluated and complemented with data from around 3,500 men in 12 countries [1520]. Of note, the distributions do not differ much from the compilation of 2010. Table 41 reports the lower reference limits for semen characteristics according to the 2010 and 2021 version of the WHO Manual.

According to the new WHO Manual, the lower fifth percentile of data from men in the reference population (Table 41) does not represent a limit between fertile and infertile men. For a general prediction of live birth *in vivo* as well as *in vitro*, a multiparametric interpretation of the entire men's and partner's reproductive potential are needed.

It has also become clear from studies that more complex testing than semen analysis may be required in everyday clinical practice, particularly in men belonging to couples with recurrent pregnancy loss from natural conception or ART and men with unexplained male infertility. Although definitive conclusions cannot be drawn, given the heterogeneity of the studies, in these patients there is evidence that sperm DNA may be damaged, thus resulting in pregnancy failure [1501, 1524, 1525] (see below).

Table 41: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	2010 Lower reference limit (95% CI)	2021 Lower reference limit (95% CI)
Semen volume (mL)	1.5 (1.4-1.7)	1.4 (1.3-1.5)
Total sperm number (10^6/ejaculate)	39 (33-46)	39 (35-40)
Sperm concentration (10^6/mL)	15 (12-16)	16 (15-18)
Total motility (PR + NP, %)	40 (38-42)	42 (40-43)
Progressive motility (PR, %)	32 (31-34)	30 (29-31)
Vitality (live spermatozoa, %)	58 (55-63)	54 (50-56)
Sperm morphology (normal forms, %)	4 (3.0-4.0)	4 (3.9-4.0)

Other consensus threshold values		
pH	> 7.2	> 7.2
Peroxidase-positive leukocytes (10^6/mL)	< 1.0	< 1.0
Tests for antibodies on spermatozoa		
MAR test (motile spermatozoa with bound particles, %)	< 50	No evidence-based reference values. Each laboratory should define its normal reference ranges by testing a sufficiently large number of normal fertile men.
Immunobead test (motile spermatozoa with bound beads, %)	≤ 50	No evidence-based reference limits.
Accessory gland function		
Seminal zinc (µmol/ejaculate)	≥ 2.4	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13	≥ 13
Seminal neutral α-glucosidase (mU/ejaculate)	≥ 20	≥ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

** Distribution of data from the population is presented with one-sided intervals (extremes of the reference population data). The lower 5th percentile represents the level under which only results from 5% of the men in the reference population were found.*

If semen analysis is normal according to WHO criteria, a single test is sufficient. If the results are abnormal on at least two tests, further andrological investigation is indicated. According to WHO reference criteria 5th end, it is important to differentiate between the following [1523]:

- oligozoospermia: < 15 million spermatozoa/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.

None of the individual sperm parameters (e.g., concentration, morphology and motility), are diagnostic per se of infertility. According to the WHO reference criteria 6th edn., this subdivision is not reported, although the EAU Guidelines panel considers this further segregation still clinically relevant in the everyday clinical practice.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-terato-zoospermia (OAT) syndrome. As in azoospermia (namely, the complete absence of spermatozoa in semen), in severe cases of oligozoospermia (spermatozoa < 5 million/mL) [1526], there is an increased incidence of obstruction of the male genital tract and genetic abnormalities. In those cases, a more comprehensive assessment of the hormonal profile may be helpful to further and more accurately differentially diagnose among pathological conditions.

In azoospermia, the semen analysis may present with normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3,000 g for 15 minutes and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically [1522]. This is to ensure that small quantities of sperm are detected, which may be potentially used for intra-cytoplasmic sperm injection (ICSI); therefore, removing the need for surgical intervention.

10.3.3 Measurement of sperm DNA Fragmentation Index (DFI)

Semen analysis is a descriptive evaluation and may be unable to discriminate between the sperm of fertile and infertile men. Therefore, it is now apparent that sperm DNA damage may occur in men with infertility. DNA fragmentation, or the accumulation of single- and double-strand DNA breaks, is a common property of sperm, and an increase in the level of sperm DNA fragmentation has been shown to reduce the chances of natural conception. Although no studies have unequivocally and directly tested the impact of sperm DNA damage on clinical management of infertile couples, sperm DNA damage is more common in infertile men and has been identified as a major contributor to male infertility, as well as poorer outcomes following ART [1527, 1528], including impaired embryo development [1527], miscarriage, recurrent pregnancy loss [1524, 1525, 1529], and birth defects [1527]. Sperm DNA damage can be increased by several factors including hormonal anomalies, varicocele, chronic infection and lifestyle factors (e.g., smoking) [1528].

Several assays have been described to measure sperm DNA damage. It has been suggested that current methods for assessing sperm DNA integrity still do not reliably predict treatment outcomes from ART and there is controversy whether to recommend them routinely for clinical use [1528, 1530]. Of those, terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labelling (TUNEL) and the alkaline comet test (COMET) directly measure DNA damage. Conversely, sperm chromatin structure assay (SCSA) and sperm chromatic dispersion test (SCD) are indirect tools for DNA fragmentation assessment. Sperm chromatin structure assay is still the most widely studied and one of the most commonly used techniques to detect DNA damage [1531, 1532]. In SCSA, the number of cells with DNA damage is indicated by the DNA fragmentation index (DFI) [1533], whereas the proportion of immature sperm with defects in the histone-to-protamine transition is indicated by high DNA stainability [1534]. It is suggested that a threshold DFI of 25% as measured with SCSA, is associated with reduced pregnancy rates via natural conception or intra-uterine insemination (IUI) [1532]. Furthermore, DFI values > 50% on SCSA are associated with poorer outcomes from in vitro fertilisation (IVF). More recently, the mean COMET score and scores for proportions of sperm with high or low DNA damage have been shown to be of value in diagnosing male infertility and providing additional discriminatory information for the prediction of both IVF and ICSI live births [1528].

Testicular sperm is reported to have lower levels of sperm DFI when compared to ejaculated sperm [1535]. Couples with elevated DNA fragmentation may benefit from combination of testicular sperm extraction (TESE) and ICSI, an approach called TESE-ICSI, which may not overcome infertility when applied to an unselected population of infertile men with untested DFI values [1532, 1535]. However, further evidence is needed to support this practice in the routine clinical setting [1535].

10.3.4 ***Hormonal determinations***

In men with testicular deficiency, hypergonadotropic hypogonadism (also called primary hypogonadism) is usually present, with high levels of FSH and LH, with or without low levels of testosterone. Generally, the levels of FSH negatively correlate with the number of spermatogonia [1536]. When spermatogonia are absent or markedly diminished, FSH level is usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH level is usually within the normal range [1536]. However, for patients undergoing TESE, FSH levels do not accurately predict the presence of spermatogenesis, as men with maturation arrest on histology can have both normal FSH and testicular volume [1537, 1538]. Furthermore men with non-obstructive azoospermia (NOA) and high levels of FSH may still harbour focal areas of spermatogenesis at the time of TESE or microdissection TESE (mTESE) [1538, 1539].

10.3.5 ***Genetic testing***

All urologists working in andrology must have an understanding of the genetic abnormalities most commonly associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with low sperm counts can still be offered a reasonable chance of paternity, using IVF, ICSI and sperm extraction from the testes in cases of azoospermia. However, the spermatozoa of infertile men show an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples. However, screening of chromosomal anomalies in spermatozoa (sperm aneuploidy) is also feasible and can be performed in selected cases (e.g., recurrent miscarriage) [1540-1542].

10.3.5.1 Chromosomal abnormalities

Chromosomal abnormalities can be numerical (e.g., trisomy) or structural (e.g., inversions or translocations). In a survey of pooled data from 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [1543]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 new-born male infants, of whom 131 (0.14%) had sex chromosomal abnormalities and 232 (0.25%) autosomal abnormalities [1543]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with sperm count < 5 million/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population [1544, 1545]. Men with NOA are at highest risk, especially for sex chromosomal anomalies (e.g., Klinefelter syndrome) [1546, 1547].

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is currently indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [1545]. This broad selection criterion has been recently externally validated, with the finding that the suggested threshold has a low sensitivity, specificity, and discrimination (80%, 37%, and 59%, respectively) [1548].

In this context, a novel nomogram, with a 2% probability cut-off, which allows for a more careful detection of karyotype alterations has been developed [1548]. Notwithstanding, the clinical value of spermatozoa < 10 million/mL remains a valid threshold until further studies, evaluating the cost-effectiveness, in which costs of adverse events due to chromosomal abnormalities (e.g., miscarriages and children with congenital anomalies) are performed [1549]. If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

10.3.5.1.1 Sex chromosome abnormalities (Klinefelter syndrome and variants [47,XXY; 46,XY/47,XX mosaicism])

Klinefelter syndrome is the most common sex chromosomal abnormality [1550]. Adult men with Klinefelter syndrome usually have small firm testes along with features of primary hypogonadism. The phenotype is the final result of a combination between genetic, hormonal and age-related factors [15]. The phenotype varies from that of a normally virilised male to one with the stigmata of androgen deficiency. In most cases infertility and reduced testicular volume are the only clinical features that can be detected. Leydig cell function is also commonly impaired in men with Klinefelter syndrome and thus testosterone deficiency is more frequently observed than in the general population [1551], although rarely observed during the peri-pubertal period, which usually occurs in a normal manner [15, 1552]. Rarely, more pronounced signs and symptoms of hypogonadism can be present, along with congenital abnormalities including heart and renal problems [1553].

The presence of germ cells and sperm production are variable in men with Klinefelter syndrome and are more frequently observed in mosaicism, 46,XY/47,XXY. Based on sperm fluorescence in situ hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI [1554]. The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter mosaicism [1555, 1556] and in 1.36-25% of men with somatic karyotype 47,XXY [1557-1560]. In patients with azoospermia, TESE or mTESE are therapeutic options as spermatozoa can be recovered in up to 50% of cases [1561, 1562]. Although the data are not unique [1562], there is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1546, 1563].

Numerous healthy children have been born using ICSI without pre-implantation genetic diagnosis (PGD) although the conception of one 47,XXY foetus has been reported [1550]. Although data published so far have not reported any difference in the prevalence of aneuploidy in children conceived using ICSI in Klinefelter syndrome compared to the general population, men with Klinefelter syndrome undergoing fertility treatments should be counselled regarding the potential genetic abnormalities in their offspring.

Regular medical follow-up of men with Klinefelter syndrome is recommended as testosterone therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed [1564]. Since this syndrome is associated with several general health problems, appropriate medical follow-up is therefore advised [16, 1565, 1566]. In particular, men with Klinefelter syndrome are at higher risk of metabolic and cardiovasculardiseases (CVD), including venous thromboembolism (VTE). Therefore, men with Klinefelter syndrome should be made aware of this risk, particularly when starting testosterone therapy [1567]. In addition, a higher risk of haematological malignancies has been reported in men with Klinefelter syndrome [16].

Testicular sperm extraction in peri-pubertal or pre-pubertal boys with Klinefelter syndrome aiming at cryopreservation of testicular spermatogonial stem cells is still considered experimental and should only be performed within a research setting [1568]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1569].

10.3.5.1.2 Autosomal abnormalities

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. As with Klinefelter syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring. However, the use of this genetic test is largely limited by the availability of laboratories able to perform this analysis [1570]. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [1571, 1572].

10.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1573]. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis. Approximately 2,000 CFTR mutations have been identified and any CFTR alteration may lead to congenital bilateral absence of the vas deferens (CBAVD). However, only those with homozygous mutations exhibit CF disease [1574]. Congenital bilateral absence of the vas deferens is a rare reason of male factor infertility, which is found 1% of infertile men and in up to 6% of men with obstructive azoospermia [1575]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be carefully examined to exclude CBAVD, particularly those with a semen volume < 1.0 mL and acidic pH < 7.0 [1576-1578]. In patients with CBAVD-only or CF, TESA, microsurgical epididymal sperm aspiration (MESA) or TESE with ICSI can be used to achieve pregnancy. However, higher sperm quality, easier sperm retrieval and better ICSI outcomes are associated with CBAVD-only patients compared with CF patients [1574].

The most frequently found mutations are F508, R117H and W1282X, but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1579, 1580]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1581], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community through the analysis of a mutation panel. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test also his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider carefully whether to proceed with ICSI using the man's sperm, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4% [1582].

10.3.5.2.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Congenital unilateral absence of the vas deferens (CUAVD) is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1583]. Consequently, in these subjects CFTR mutation screening is not indicated. Men with CUAVD are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. Cystic fibrosis transmembrane conductance regulator gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. The prevalence of renal anomalies is rare for patients who have CBAVD and CFTR mutations [1584]. Abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CFTR mutations. Findings may range from CUAVD with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1585].

10.3.5.3 Y microdeletions – partial and complete

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc deletions [1586]. Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia [1587]. In each AZF region, there are several spermatogenesis candidate genes [1588]. Deletions occur *en bloc* (i.e., removing more than one gene), it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a "fine tuner" of sperm production, and its specific screening is not advised [1589]. It has been observed that a number of commercial laboratories can use a limited number of primer sets over the AZF a, b and c regions in their Y chromosome microdeletion assay. This can eventually miss smaller microdeletions and clinicians should be aware over the managing work-up of patients scheduled for testicular surgery [1590, 1591].

10.3.5.3.1 Clinical implications of Y microdeletions

The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure [1592].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men [1593, 1594].

- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%) [1595].
- AZFc deletions are most common (65-70%), followed by Y-deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%) [1596].
- Complete deletion of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete deletions of the AZFb region is associated with spermatogenic arrest. Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm at the time of TESE and sperm is not found in these patients. Therefore, TESE should not be attempted in these patients [1597, 1598].
- Deletions of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Sperm can be found in 50-75% of men with AZFc microdeletions [1597-1599].
- Men with AZFc microdeletions who are oligo-zoospermic or in whom sperm is found at the time of TESE must be counselled that any male offspring will inherit the deletion.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [1595, 1600].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [1600].

10.3.5.3.1.1 Testing for Y microdeletions

Historically, indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). A recent meta-analysis assessing the prevalence of microdeletions on the Y chromosome in oligo-zoospermic men in 37 European and North American studies (n = 12,492 oligo-zoospermic men) showed that the majority of microdeletions occurred in men with sperm concentrations ≤ 1 million sperm/mL, with < 1% identified in men with > 1 million sperm/mL [1595]. In this context, while an absolute threshold for clinical testing cannot be universally given, patients may be offered testing if sperm counts are < 5 million sperm/mL, but must be tested if ≤1 million sperm/mL.

With the efforts of the European Academy of Andrology (EAA) guidelines and the European Molecular Genetics Quality Network external quality control programme (http://www.emqn.org/emqn/), Yq testing has become more reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions [1601].

10.3.5.3.1.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son will have the same microdeletion [1601], but occasionally the son may have a more extensive deletion [1602]. The extent of spermatogenic failure (still in the range of azoo-/oligo-zoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity on reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [1603, 1604], indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [1605]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [1600, 1601]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype.

10.3.5.3.1.3 Y-chromosome: 'gr/gr' deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [1606]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5-8 fold increased risk for oligozoospermia [1601, 1607-1609]. The frequency of gr/gr deletion in oligozoospermic patients is ~5% [1610].

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [1608-1610]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary among different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplo-groups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multi-centre study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [1581]. However, these data need confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noting that partial AZFc deletions, gr/gr and b2/b3, may predispose to complete AZFc deletion in the next generation [1611].

10.3.5.3.1.4 Autosomal defects with severe phenotypic abnormalities and infertility

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (e.g., Prader-Willi syndrome [1612], Bardet-Biedl syndrome [1613], Noonan's syndrome, Myotonic dystrophy, dominant polycystic kidney disease [1614, 1615], and 5 α-reductase deficiency [1616-1619], etc.) Pre-implantation genetic screening may be necessary in order to improve the ART outcomes among men with autosomal chromosomal defects [1620, 1621].

10.3.5.4 Sperm chromosomal abnormalities

Sperm can be examined for their chromosomal constitution using FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [1543, 1622-1624] and with translocations and may lead to recurrent pregnancy loss (RPL) or recurrent implantation failure [1625]. In a large retrospective series, couples with normal sperm FISH had similar outcomes from IVF and ICSI on pre-implantation genetic screening (PGS). However, couples with abnormal FISH had better clinical outcomes after PGS, suggesting a potential contribution of sperm to aneuploidic abnormalities in the embryo [1626]. In men with sperm aneuploidy, PGS combined with IVF and ICSI can increase chances of live births [1542].

10.3.5.5 Measurement of Oxidative Stress

Oxidative stress is considered to be central in male infertility by affecting sperm quality, function, as well as the integrity of sperm [1627]. Oxidative stress may lead to sperm DNA damage and poorer DNA integrity, which are associated with poor embryo development, miscarriage and infertility [1628, 1629]. Spermatozoa are vulnerable to oxidative stress and have limited capacity to repair damaged DNA. Oxidative stress is generally associated with poor lifestyle (e.g., smoking) and environmental exposure, and therefore antioxidant regimens and lifestyle interventions may reduce the risk of DNA fragmentation and improve sperm quality [1630]. However, these data have not been supported by RCTs. Furthermore, there are no standardised testing methods for ROS and the duration of antioxidant treatments. Although ROS can be measured by various assays (e.g., chemiluminescence), routine measurement of ROS testing should remain experimental until these tests are validated in RCTs [1631].

10.3.5.6 Outcomes from assisted reproductive technology and long-term health implications to the male and offspring

It is estimated that > 4 million babies have been born with ART since the first baby was conceived by IVF in 1978 [1632]. As the number of couples undergoing ART has increased [1633, 1634], safety concerns related to ART have been raised. Assisted reproductive technology-conceived offspring have poorer prenatal outcomes, such as lower birth weight, lower gestational age, premature delivery, and higher hospital admissions compared with naturally conceived offspring [1635, 1636]. However, the exact mechanisms resulting in these complications remain obscure. Birth defects have also been associated with children conceived via ART [1637-1639]. Meta-analyses have shown a 30-40% increase in major malformations linked with ART [1640-1642]. However, debate continues as to whether the increased risk of birth defects are related to parental age, ART or the intrinsic defects in spermatogenesis in infertile men [1643-1648].

As for the long-term outcomes, post-natal growth patterns are mostly not associated with ART [1637, 1649, 1650]. However, a number of studies have shown that ART children are taller [1651, 1652]. This may be important as there is evidence showing that rapid weight gain during early childhood is linked with higher blood pressure levels in children conceived via ART [1653]. It is also suggested that ART-conceived children have similar childhood illnesses and hospital services rates as compared with naturally conceived children [1654-1656]. Some studies have shown an increased risk of retinoblastoma [1657] and hepatoblastoma in children after ART. However, these studies have been challenged with other studies that have not supported these findings [1658]. The current evidence for cancer risk in children conceived with ART is inadequate and further studies are warranted [1659, 1660]. Finally, several epigenetic alterations seem to be caused by ART, which might be the molecular basis to some complex traits and diseases [1661].

10.3.6 ***Imaging in infertile men***

In addition to physical examination, a scrotal US may be helpful in: (i) measuring testicular volume; (ii) assessing testicular anatomy and structure in terms of US patterns, thus detecting signs of testicular dysgenesis often related to impaired spermatogenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testicular tumours; and, (iii) finding indirect signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) [1516]. In clinical practice, Prader's orchidometer-derived testicular volume is considered a reliable surrogate of US-measured testicular volume, easier to perform and cost-effective [1515]. Nevertheless, scrotal US has a relevant role in testicular volume

assessment when Prader's orchidometer is unreliable (e.g., large hydrocele, inguinal testis, epididymal enlargement/fibrosis, thickened scrotal skin; small testis, where the epididymis is large in comparison to the total testicular volume [1515, 1516]). Ultrasound-patterns of testicular inhomogeneity [1662, 1663] is usually associated with ageing, although it has also been reported in association with testicular atrophy and fibrosis [1516]. At present, a diagnostic testicular biopsy is not recommended when testicular inhomogeneity is detected [1662, 1663].

10.3.6.1 Scrotal US

Scrotal US is widely used in everyday clinical practice in patients with oligo-zoospermia or azoospermia, as infertility has been found to be an additional risk factor for testicular cancer [1664, 1665]. It can be used in the diagnosis of several diseases causing infertility including testicular neoplasms and varicocele.

10.3.6.1.1 Testicular neoplasms

In one study, men with infertility had an increased risk of testicular cancer (hazard ratio [HR] 3.3). When infertility was refined according to individual semen parameters, oligo-zoospermic men had an increased risk of cancer compared with fertile control subjects (HR 11.9) [1666]. In a recent systematic review infertile men with testicular microcalcification (TM) were found to have a ~18-fold higher prevalence of testicular cancer [1667]. However, the utility of US as a routine screening tool in men with infertility to detect testicular cancer remains a matter of debate [1664, 1665].

One issue in undertaking routine screening for testicular neoplasms in this cohort of patients is the risk of overdiagnosis and the increased detection of indeterminate lesions of the testis. These testicular lesions are often detected during the diagnostic work-up of infertile men and are difficult to characterise as benign or malignant based only upon US criteria, including size, vascularity and echogenicity.

A dichotomous cut-off of certainty in terms of lesion size that may definitely distinguish benign from malignant testicular masses is currently not available. However, in a study with 81 patients with a lesion size < 10 mm, on histology showed that 56 (69%) were benign lesions, although one-third were malignant. All lesions < 5 mm in diameter were benign [1668]. Available data suggest that the smaller the lesion, the less likely that it is malignant [1669], and lesions < 5 mm could be monitored, as they have a low probability of malignancy.

Small hypoechoic/hyperechoic areas may be diagnosed as intra-testicular cysts, focal Leydig cell hyperplasia, fibrosis and focal testicular inhomogeneity after previous pathological conditions. Hence, they require careful periodic US assessment and follow-up, especially if additional risk factors for malignancy are present (i.e., infertility, bilateral TM, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of/contralateral tumour) [1516].

In the case of interval growth of a lesion and/or the presence of additional risk factors for malignancy, testicular biopsy/surgery may be considered, although the evidence for adopting such a management policy is limited. In 145 men referred for azoospermia who underwent US before testicular biopsy, 49 (34%) had a focal sonographic abnormality; a hypoechoic lesion was found in 20 patients (14%), hyperechoic lesions were seen in 10 patients (7%); and, a heterogeneous appearance of the testicular parenchyma was seen in 19 patients (13%). Of 18 evaluable patients, 11 had lesions < 5 mm; all of which were confirmed to be benign. All other patients with hyperechoic or heterogeneous areas on US with subsequent tissue diagnoses were found to have benign lesions. The authors concluded that men with severe infertility who have incidental testicular lesions, negative tumour markers and lesions < 5 mm may be observed with serial scrotal US examinations and enlarging lesions or those of greater dimension can be considered for histological biopsy [1670].

Other studies have suggested that if a testicular lesion is hyperechoic and non-vascular on colour Doppler US and associated with negative tumour markers, the likelihood of malignancy is low and consideration can be given to regular testicular surveillance, as an alternative to radical surgery. In contrast, hypoechoic and vascular lesions are more likely to be malignant [1671-1675]. However, most lesions cannot be characterised by US (indeterminate), and histology remains the only certain diagnostic tool. A multidisciplinary team discussion (MDT), including invasive diagnostic modalities, should therefore be considered in these patients.

The role of US-guided intra-operative frozen section analysis in the diagnosis of testicular cancer in indeterminate lesions remains controversial, although several authors have proposed its value in the intra-operative diagnosis of indeterminate testicular lesions [1676]. Although the default treatment after patient counselling and MDT discussion may be radical orchidectomy, an US-guided biopsy with intra-operative frozen section analysis may be offered as an alternative to radical orchidectomy and potentially obviate the

need for removal of the testis in a patient seeking fertility treatment or is hypogonadal. In men who have severe abnormalities in semen parameters (e.g., azoospermia), a concurrent mTESE can also be performed at the time of diagnostic biopsy.

In summary, if an indeterminate lesion is detected incidentally on US in an infertile man, MDT discussion is highly recommended. Based upon the current literature, lesions < 5mm in size are likely to be benign and serial US and self-examination can be performed. However, men with larger sized lesions (> 5mm), which are hypoechoic or demonstrate vascularity, may be considered for open US-guided testicular biopsy, testis sparing surgery with tumour enucleation for frozen section examination or radical orchidectomy. Therefore, in making a definitive treatment decision for surveillance vs. intervention, consideration should be given to the size of the lesion, echogenicity, vascularity and previous history (e.g., cryptorchidism, previous history of germ cell tumour [GCT]). If intervention is to be undertaken in men with severe hypospermatogenesis (e.g., azoospermia), then a simultaneous TESE can be undertaken, along with sperm banking.

10.3.6.1.2 Varicocele

At present, the clinical management of varicocele is still mainly based on physical examination; nevertheless, scrotal colour Doppler US is useful in assessing venous reflux and diameter, when palpation is unreliable and/or in detecting recurrence/persistence after surgery [1516]. Definitive evidence of reflux and venous diameter may be utilised in the decision to treat (see Section 10.4.3.1 and 10.4.3.2).

10.3.6.1.3 Other

Scrotal US is able to detect changes in the proximal part of the seminal tract due to obstruction. Especially for CBAVD patients, scrotal US is a favourable option to detect the abnormal appearance of the epididymis. Given that, three types of epididymal findings are described in CBAVD patients: tubular ectasia (honeycomb appearance), meshwork pattern, and complete or partial absence of the epididymis [1677, 1678].

10.3.6.2 Transrectal US

For patients with a low seminal volume, acidic pH and severe oligozoospermia or azoospermia, in whom obstruction is suspected, scrotal and transrectal US are of clinical value in detecting CBAVD and presence or absence of the epididymis and/or seminal vesicles (SV) (e.g., abnormalities/agenesis). Likewise, transrectal US (TRUS) has an important role in assessing obstructive azoospermia (OA) secondary to CBAVD or anomalies related to the obstruction of the ejaculatory ducts, such as ejaculatory duct cysts, seminal vesicular dilatation or hypoplasia/atrophy, although retrograde ejaculation should be excluded as a differential diagnosis [1516, 1679].

*10.3.7 **Recommendations for the diagnostic work-up of male infertility***

Recommendations	**Strength rating**
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention).	Strong
A complete medical history, physical examination and semen analysis are the essential components of male infertility evaluation.	Strong
Prader's orchidometer-derived testicular volume is a reliable surrogate of ultrasound (US)-measured testicular volume in everyday clinical practice.	Weak
Perform semen analyses according to the most recent WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edn.) indications and reference criteria or according to the previous version (5th edn.) until a formal and complete adoption of the newly-released parameters will be implemented.	Strong
Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
Include counselling for infertile men or men with abnormal semen parameters of the associated health risks.	Weak
In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle Stimulating Hormone/Luteinising Hormone.	Weak
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Do not test for Y-chromosome microdeletions in men with pure obstructive azoospermia as spermatogenesis will be normal.	Strong

Y-chromosome microdeletion testing may be offered in men with sperm concentrations of < 5 million sperm/mL, but must be mandatory in men with sperm concentrations of ≤ 1 million sperm/mL.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intra-cytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters.	Strong
Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for cystic fibrosis transmembrane conductance regulator gene mutations, which should include common point mutations and the 5T allele.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For men with Klinefelter syndrome, offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility.	Strong
Perform scrotal US in patients with infertility, as there is a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testicular biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak
Perform transrectal US if a partial or complete distal obstruction is suspected.	Strong
Consider imaging for renal abnormalities in men with structural abnormalities of the vas deferens and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.	Strong

10.4 Special Conditions and Relevant Clinical Entities

*10.4.1 **Cryptorchidism***

Cryptorchidism is the most common congenital abnormality of the male genitalia; at 1 year of age nearly 1% of all full-term male infants have cryptorchidism [1680]. Approximately 30% of undescended testes are non-palpable and may be located within the abdominal cavity. These guidelines will only deal with management of cryptorchidism in adults.

10.4.1.1 Classification

The classification of cryptorchidism is based on the duration of the condition and the anatomical position of the testes. If the undescended testis has been identified from birth then it is termed congenital while diagnosis of acquired cryptorchidism refers to men that have been previously noted to have testes situated within the scrotum. Cryptorchidism is categorised on whether it is bilateral or unilateral and the location of the testes (inguinal, intra-abdominal or ectopic).

Studies have shown that treatment of congenital and acquired cryptorchidism results in similar hormonal profiles, semen analysis and testicular volumes [1681, 1682]. However, testicular volume and hormonal function are reduced in adults treated for congenital bilateral cryptorchidism compared to unilateral cryptorchidism [1683].

10.4.1.1.1 Aetiology and pathophysiology

It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy, including exposure to endocrine disrupting chemicals. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig/Sertoli cell dysfunction [1684]. Cryptorchidism has also been linked with maternal gestational smoking [1685] and premature birth [1686].

10.4.1.1.2 Pathophysiological effects in maldescended testes

10.4.1.1.2.1 Degeneration of germ cells

The degeneration of germ cells in maldescended testes is apparent even after the first year of life and varies, depending on the position of the testes [1687]. During the second year, the number of germ cells declines. Early treatment is therefore recommended (surgery should be performed within the subsequent year) to conserve spermatogenesis and hormone production, as well as to decrease the risk for tumours [1688]. Surgical treatment is the most effective. Meta-analyses on the use of medical treatment with GnRH and hCG have demonstrated poor success rates [1689, 1690]. It has been reported that hCG treatment may be harmful to future spermatogenesis; therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend it use on a routine basis [1691]. See also the EAU Guidelines on Paediatric Urology [1692].

There is increasing evidence to suggest that in unilateral undescended testis, the contralateral normal descended testis may also have structural abnormalities, including smaller volume, softer consistency and reduced markers of future fertility potential (spermatogonia/tubule ratio and dark spermatogonia) [1681, 1693]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

10.4.1.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [1694]. Early surgical treatment may have a positive effect on subsequent fertility [1695]. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity falls to 35-53% [1696]. It is also important to screen for hypogonadism, as this is a potential long-term sequelae of cryptorchidism and could contribute to impaired fertility and potential problems such as testosterone deficiency and MetS [1697].

10.4.1.1.2.3 Germ cell tumours

As a component of TDS, cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcifications and intratubular germ cell neoplasia *in situ* (GCNIS), formerly known as carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [1698]. The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour [1680]. Orchidopexy performed before the onset of puberty has been reported to decrease the risk of testicular cancer [1699]. However, there is evidence to suggest that even men who undergo early orchidopexy still harbour a higher risk of testicular cancer than men without cryptorchidism [1700]. Therefore all men with a history of cryptorchidism should be warned that they are at increased risk of developing testicular cancer and should perform regular testicular self-examination [1701]. There is also observational study data suggesting that cryptorchidism may be a risk factor for worsening clinical stage of seminoma but this needs to be substantiated with future prospective studies [1702].

10.4.1.2 Disease management

10.4.1.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood. Although some studies have recommended the use of hormonal stimulation as an adjunct to orchidopexy to improve fertility preservation, there is a lack of long-term data and concerns regarding impairment to spermatogenesis with the use of these drugs [1703].

10.4.1.2.2 Surgical treatment

In adolescence, removal of an intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the risk of malignancy [1704]. In adults, with a palpable undescended testis and a normal functioning contralateral testis (i.e., biochemically eugonadal), an orchidectomy may be offered as there is evidence that the undescended testis confers a higher risk of GCNIS and future development of GCT [1705] and regular testicular self-examination is not an option in these patients. In patients with unilateral undescended testis (UDT) and impaired testicular function on the contralateral testis as demonstrated by biochemical hypogonadism and/or impaired sperm production (infertility), an orchidopexy may be offered to preserve androgen production and fertility. However, based on Panel consensus multiple biopsies of the UDT are recommended at the time of orchidopexy to exclude intra-testicular GCNIS as a prognostic indicator of future development of GCT. As indicated above, the correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men and therefore may be considered in these patients or in patients who place a high value on fertility preservation [1706]. Vascular damage is

the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the post-operative atrophy rate was 12% in cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [1707]. At the time of orchidectomy in the treatment of GCT, biopsy of the contralateral testis should be offered to patients at high risk for GCNIS (i.e., history of cryptorchidism, < 12 mL testicular volume, poor spermatogenesis [1708]).

10.4.1.3 Summary of evidence recommendations for cryptorchidism

Summary of evidence	LE
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.	2a
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and GCTs and patients should be counselled appropriately.	2b
Paternity in men with unilateral cryptorchidism is almost equal to men without cryptorchidism.	1b
Bilateral cryptorchidism significantly reduces the likelihood of paternity and patients should be counselled appropriately.	1b

Recommendations	Strength rating
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*).	Strong
Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible.	Weak

*10.4.2 **Germ cell malignancy and male infertility***

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of sub-fertile men [1709]. The lifetime risk of TGCT varies among ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and non-seminomas are preceded by GCNIS, and untreated GCNIS eventually progresses to invasive cancer [1710-1712]. There has been a general decline in male reproductive health and an increase in testicular cancer in western countries [1713, 1714]. In almost all countries with reliable cancer registries, the incidence of testicular cancer has increased [1600, 1715]. This has been postulated to be related to TDS, which is a developmental disorder of the testes caused by environmental and/or genetic influences in pregnancy. As detailed above, the adverse sequelae of TDS include cryptorchidism hypospadias, infertility and an increased risk of testicular cancer [1684]. Endocrine disrupting chemicals have also been associated with sexual dysfunction [1716] and abnormal semen parameters [1717]. These cancers arise from premalignant gonocytes or GCNIS [1718]. Testicular microcalcification, seen on US, can be associated with TGCT and GCNIS of the testes [1667, 1719, 1720].

10.4.2.1 Testicular germ cell cancer and reproductive function

Sperm cryopreservation is considered standard practice in patients with cancer overall, and not only in those with testicular cancer [1721, 1722]. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery that may impair spermatogenesis or ejaculation (i.e., chemotherapy, radiotherapy or retroperitoneal surgery).

Men with TGCT have decreased semen quality, even before cancer treatment. Azoospermia has been observed in 5–8% of men with TGCT [1723] and oligospermia in 50% [1724]. Given that the average 10-year survival rate for testicular cancer is 98% and it is the most common cancer in men of reproductive potential, it is mandatory to include counselling regarding fertility preservation prior to any gonadotoxic treatment [1724, 1725]. Semen analysis and cryopreservation are therefore recommended prior to any gonadotoxic cancer treatment and all patients should be offered cryopreservation of ejaculated sperm or sperm extracted surgically (e.g., c/mTESE) if shown to be azoospermic or severely oligozoospermic. Given that a significant number of men with testicular cancer at the time of first presentation have severe semen abnormalities (i.e., severe

oligozoospermia/azoospermia) even prior to any treatment [1718], it is recommended that men should undergo sperm cryopreservation prior to orchidectomy. As mentioned above, in those who are either azoospermic or severely oligo-zoospermic this will allow an opportunity to perform TESE prior to further potential gonadotoxic/ablative surgery [1724]. The use of cryopreservation has been demonstrated to be the most cost effective strategy for fertility preservation in patients undergoing potential gonadotoxic treatments [1726, 1727]. In cases of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (onco-TESE) potential. The surgical principles in onco-TESE do not differ from the technique of mTESE for men with infertility (e.g., NOA) [1728, 1729]. In this context, referral to a urologist adept in microsurgery is desirable with facilities for sperm cryopreservation.

Rates of under-utilisation of semen analysis and sperm cryopreservation have been reported to be high; resulting in the failure to identify azoospermic or severely oligozoospermic patients at diagnosis who may eventually benefit from fertility-preserving procedures (e.g., onco-mTESE at the time of orchidectomy). Therefore, counselling about fertility preservation is a priority and needs to be broached earlier in men with testicular cancer [1724]. There are controversial arguments that performing cryopreservation prior to orchidectomy may delay subsequent treatment and have an adverse impact on survival. In this context, orchidectomy should not be unduly delayed if there are no facilities for cryopreservation or there is a potential delay in treatment.

Treatment of TGCT can result in additional impairment of semen quality [1730] and increased sperm aneuploidy up to two years following gonadotoxic therapy [1731]. Chemotherapy is also associated with DNA damage and an increased DNA fragmentation rate [1732]. However, sperm aneuploidy levels often decline to pre-treatment levels 18-24 months after treatment [1731]. Several studies reviewing the offspring of cancer survivors have not shown a significant increased risk of genetic abnormalities in the context of chemotherapy and radiotherapy [1733].

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [1734]. The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol may help to stratify those patients at increased risk of hypogonadism and provide a baseline for post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should be advised that they may be at increased risk of developing hypogonadism, as a result of an age-related decrease in testosterone production and could potentially develop MetS; there are no current long-term data supporting this. The risk of hypogonadism is increased in the survivors of testicular cancer and serum testosterone levels should be evaluated during the management of these patients [1735]. However, this risk is greatest at 6-12 months post-treatment and suggests that there may be some improvement in Leydig cell function after treatment. Therefore it is reasonable to delay initiation of testosterone therapy, until the patient shows continuous signs or symptoms of testosterone deficiency [1710]. The risk of low libido and ED is also increased in TGCT patients [1736]. Patients treated for TGCT are also at increased risk of CVD [1732]. Therefore, patients may require a multi-disciplinary therapy approach and, in this context, survivorship programmes incorporating a holistic view of patients considering psychological, medical and social needs could be beneficial. In patients who place a high value on fertility potential, the use of testosterone therapy in men with symptoms suggestive for TDS needs to be balanced with worsening spermatogenesis. In these patients consideration can be given to the use of selective oestrogen receptor modulators (SERMs; e.g., clomiphene) or gonadotrophin analogues (e.g., hCG), although these are off-label treatments in this particular clinical setting.

10.4.2.2 Testicular microcalcification (TM)

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [1737, 1738]. Although the true incidence of TM in the general population is unknown, it is most probably rare. Ultrasound findings of TM have been seen in men with TGCT, cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter syndrome, hypogonadism, male pseudohermaphroditism and varicocele [1685]. The incidence reported seems to be higher with high-frequency US machines [1739]. The relationship between TM and infertility is unclear, but may relate to testicular dysgenesis, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification with hydroxyapatite occurs. Testicular microcalcification is found in testes at risk of malignant development, with a reported incidence of TM in men with TGCT of 6-46% [1740-1742]. A recent systematic review and meta-analysis of case-control studies indicated that the presence of TM is associated with a ~18-fold higher odds ratio for testicular cancer in infertile men (pooled OR: 18.11, 95% CI: 8.09, 40.55; $p < 0.0001$) [1667].

Testicular microcalcification should therefore be considered pre-malignant in this setting and patients counselled accordingly. Testicular biopsies from men with TM have found a higher prevalence of GCNIS, especially in those with bilateral microcalcifications [1743]. However, TM can also occur in benign testicular conditions and the microcalcification itself is not malignant. Therefore, the association of TM and TGCT is controversial and the challenge is to identify those men at risk of harbouring GCNIS and future risk of TGCT. Further investigation of the association between TM and GCNIS requires testicular biopsies in large series of men without signs of TGCT with or without risk factors for TGCT. However, clinicians and patients should be reassured that testicular cancer does not develop in most men with asymptomatic TM [1720]. Available data indicate that only men in whom TM is found by US, and who have an increased risk of TGCT, should be offered testicular biopsy to exclude GCNIS. Men potentially at high-risk of harbouring or developing GCNIS include those with infertility, atrophic testes, undescended testes, history of TGCT, and contralateral TM and it has been suggested that men with these risk factors could be offered testicular biopsy [1714, 1719]. The normal mean testicular volume is estimated to be 12-30 mL and < 12 mL is considered small [1737]. Patients with a history of TGCT and TM in the contralateral testis and sub-fertile patients have been demonstrated to have an increased risk of GCNIS [1720], while there are only a few studies showing a further increase in GCNIS with TM in the context of cryptorchidism [1714, 1738, 1744]. A useful algorithm has been proposed [1714] to stratifying those patients at increased risk of GCNIS who may benefit from testicular biopsy. However, when undertaking a biopsy in this setting, the full risks and complications of adopting this strategy must be explained to the patient. With the lack of availability of large cohort studies, these recommendations must be treated with caution given the risk of overtreatment (i.e., biopsy) in these patients.

Decastro *et al.* [1745] suggested that testicular cancer would not develop in most men with TM (98.4%) during a 5-year follow-up. As such, an extensive screening programme would only benefit men at significant risk. In this context it would be prudent to advise patients with TM and risk factors for testicular cancer to at least undergo regular testicular examination. It has been suggested that these patients could also be offered annual physical examination by a urologist and US follow-up, although follow-up protocols may be difficult to implement in this invariably young cohort of patients [1685]. As testicular atrophy and infertility have an association with testicular cancer, some authors recommend biopsy or follow-up US if TM is seen [1714]. However, most patients who are azoospermic will be undergoing therapeutic biopsy (i.e., with the specific purpose of sperm retrieval) and therefore a definitive diagnosis can be made and there is a lack of evidence demonstrating a higher prevalence of testicular cancer in patients with both TM and testicular atrophy. In patients with incidental TM, the risk of GCNIS is low and a logical approach is to instruct patients to perform regular testicular self-examination.

10.4.2.3 Recommendations for germ cell malignancy and testicular microcalcification

Recommendations	**Strength rating**
Men with testicular microcalcification (TM) should learn to perform self-examination even without additional risk factors, as this may result in early detection of testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound (US), measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (< 12 mL), history of undescended testes and TGCT.	Weak
If there are suspicious findings on physical examination or US in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multi-disciplinary meeting and discussion with the patient.	Strong
Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular risk. Men should be managed in a multi-disciplinary team setting with a dedicated late-effects clinic.	Weak
Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak
Men with testicular cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction (onco-TESE) at the time of radical orchidectomy.	Weak

10.4.3 ***Varicocele***

Varicocele is a common congenital abnormality, that may be associated with the following andrological conditions:

- male sub-fertility;
- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- hypogonadism.

10.4.3.1 Classification

The following classification of varicocele [1497] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsalva manoeuvre, but can be shown by special tests (Doppler US).
- Grade 1: palpable during Valsalva manoeuvre.
- Grade 2: palpable at rest.
- Grade 3: visible and palpable at rest.

Overall, the prevalence of varicocele in one study was 48%. Of 224 patients, 104 had unilateral and 120 had bilateral varicocele; 62 (13.30%) were grade 3, 99 (21.10%) were grade 2, and 63 (13.60%) were grade 1 [1746]. Worsening semen parameters are associated with a higher grade of varicocele and age [1747, 1748].

10.4.3.2 Diagnostic evaluation

The diagnosis of varicocele is made by physical examination and Scrotal Doppler US is indicated if physical examination is inconclusive or semen analysis remains unsatisfactory after varicocele repair to identify persistent and recurrent varicocele [1497, 1749]. A maximum venous diameter of > 3 mm in the upright position and during the Valsalva manoeuvre and venous reflux with a duration > 2 seconds correlate with the presence of a clinically significant varicocele [1750, 1751]. To calculate testicular volume Lambert's formula (V=L x W x H x 0.71) should be used, as it correlates well with testicular function in patients with infertility and/or varicocele [1752]. Patients with isolated, clinical right varicocele should be examined further for abdominal, retroperitoneal and congenital pathology and anomalies.

10.4.3.3 Basic considerations

10.4.3.3.1 Varicocele and fertility

Varicocele is present in almost 15% of the normal male population, in 25% of men with abnormal semen analysis and in 35-40% of men presenting with infertility [1497, 1747, 1753, 1754]. The incidence of varicocele among men with primary infertility is estimated at 35–44%, whereas the incidence in men with secondary infertility is 45–81% [1497, 1754].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased overall survival and DNA damage [1754].

A meta-analysis showed that improvements in semen parameters are usually observed after surgical correction in men with abnormal parameters [1755]. Varicocelectomy can also reverse sperm DNA damage and improve OS levels [1753, 1754].

10.4.3.3.2 Varicocelectomy

Varicocele repair has been a subject of debate for several decades. A meta-analysis of RCTs and observational studies in men with only clinical varicoceles has shown that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen parameters, including men with NOA with hypo-spermatogenesis or late maturation (spermatid) arrest on testicular pathology [1753, 1756-1759]. Pain resolution after varicocelectomy occurs in 48-90% of patients [1760]. A recent systematic review has shown greater improvement in higher-grade varicoceles and this should be taken into account during patient counselling [1761].

In RCTs, varicocele repair in men with a subclinical varicocele was ineffective at increasing the chances of spontaneous pregnancy [1762]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found to favour treatment over observation. A Cochrane review from 2012 concluded that there is evidence to suggest that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of spontaneous pregnancy [1763]. Two recent meta-analyses of RCTs comparing treatment to observation in men with a clinical varicocele, oligozoospermia and

otherwise unexplained infertility, favoured treatment, with a combined OR of 2.39-4.15 (95% CI: 1.56-3.66 and 95% CI: 2.31-7.45, respectively) [1759, 1763]. Average time to improvement in semen parameters is up to two spermatogenic cycles [1764, 1765] with spontaneous pregnancy occurring between 6 and 12 months after varicocelectomy [1766, 1767]. A further meta-analysis has reported that varicocelectomy may improve outcomes following ART in oligozoospermic men with an OR of 1.69 (95% CI: 0.95-3.02) [1768].

10.4.3.3.3 Prophylactic varicocelectomy

In adolescents with a varicocele, there is a significant risk of over-treatment because most adolescents with a varicocele have no problem achieving pregnancy later in life [1769]. Prophylactic treatment is only advised in case of documented testicular growth deterioration confirmed by serial clinical or Doppler US examinations and/or abnormal semen analysis [1770, 1771].

More novel considerations for varicocelectomy in patients with NOA, hypogonadism and DNA damage are described below:

Varicocelectomy and NOA

Several studies have suggested that varicocelectomy may lead to sperm appearing in the ejaculate in men with azoospermia. In one such study, microsurgical varicocelectomy in men with NOA led to sperm in the ejaculate post-operatively with an increase in ensuing natural or assisted pregnancies [1772]. There were further beneficial effects on sperm retrieval rates (SRRs) and ICSI outcomes. Meta-analyses have further corroborated these findings; 468 patients diagnosed with NOA and varicocele underwent surgical varicocele repair or percutaneous embolisation. In patients who underwent varicocelectomy, SRRs increased compared to those without varicocele repair (OR: 2.65; 95% CI: 1.69-4.14; $p < 0.001$). In 43.9% of the patients (range: 20.8%-55.0%), sperm were found in post-operative ejaculate. These findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR, and overall, 44% of the treated men have sperm in the ejaculate and may avoid sperm retrieval. However, the quality of evidence available is low and the risks and benefits of varicocele repair must be discussed fully with the patient with NOA and a clinically significant varicocele prior to embarking upon treatment intervention [1757]. This must necessarily take into consideration the infertile couple together, especially considering the time needed for a possible SRR and the baseline characteristics of the female partner (i.e., age, medical history, anti-Müllerian hormone (AMH) levels = good ovarian reserve, etc.).

Varicocelectomy and hypogonadism

Evidence also suggests that men with clinical varicoceles who are hypogonadal may benefit from varicocele intervention. One meta-analysis studied the efficacy of varicocele intervention by comparing the pre-operative and post-operative serum testosterone of 712 men. The combined analysis of seven studies demonstrated that the mean post-operative serum testosterone improved by 34.3 ng/dL (95% CI: 22.57-46.04, $p < 0.00001$, $I^2 = 0\%$) compared with their pre-operative levels. An analysis of surgery vs. untreated control results showed that mean testosterone among hypogonadic patients increased by 105.65 ng/dL (95% CI: 77.99-133.32 ng/dL), favouring varicocelectomy [1773]. However, results must be treated with caution and adequate cost-benefit analysis must be undertaken to determine the risks and benefits of surgical intervention over testosterone therapy in this setting. Although, varicocelectomy may be offered to hypogonadal men with clinically significant varicoceles, patients must be advised that the full benefits of treatment in this setting must be further evaluated with prospective RCTs.

10.4.3.3.4 Varicocelectomy for assisted reproductive technology and raised DNA fragmentation

Varicocelectomy can improve sperm DNA integrity, with a mean difference of -3.37% (95% CI: -2.65% to -4.09%) [1769]. There is now increasing evidence that varicocele treatment may improve DNA fragmentation and outcomes from ART [1768, 1769]. As a consequence, more recently it has been suggested that the indications for varicocele intervention should be expanded to include men with raised DNA fragmentation. If a patient has failed ART (e.g., failure of implantation, embryogenesis or recurrent pregnancy loss) there is an argument that if DNA damage is raised, consideration could be given to varicocele intervention after extensive counselling [1774], and exclusion of other causes of raised DNA fragmentation [1769, 1775].The dilemma is whether varicocele treatment is indicated in men with raised DNA fragmentation and normal semen parameters.

In a meta-analysis of non-azoospermic infertile men with clinical varicocele by Estevez *et al.*, four retrospective studies were included of men undergoing ICSI, and included 870 cycles (438 subjected to ICSI with prior varicocelectomy, and 432 without prior varicocelectomy). There was a significant increase in the clinical pregnancy rates (OR = 1.59, 95% CI: 1.19-2.12, I2 = 25%) and live birth rates (OR = 2.17, 95%

CI: 1.55-3.06, I^2 = 0%) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy. A further study evaluated the effects of varicocele repair and its impact on pregnancy and live birth rates in infertile couples undergoing ART in male partners with oligo-azoospermia or azoospermia and a varicocele [1768]. In 1,241 patients, a meta-analysis demonstrated that varicocelectomy improved live birth rates for the oligospermic (OR = 1.699) men and combined oligo-azoospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligo-azoospermic/azoospermic groups (OR = 1.760). Live birth rates were higher for patients undergoing IUI after intervention (OR = 8.360).

10.4.3.4 Disease management

Several treatments are available for varicocele (Table 42). Current evidence indicates that microsurgical varicocelectomy is the most effective among the different varicocelectomy techniques [1769, 1776]. Unfortunately, there are no large prospective RCTs comparing the efficacy of the various interventions for varicocele. However, microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques based upon case series [1777]; however, this procedure requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation appear to be higher [1778].

Radiological techniques (sclerotherapy and embolisation) are minimally invasive widely used approaches, although higher recurrence rates compared to microscopic varicocelectomy have been reported (4-27%) [1754]. Robot-assisted varicocelectomy has a similar success rate compared to the microscopic varicocelectomy technique, although larger prospective randomised studies are needed to establish the most effective method [1779-1781].

Table 42: Recurrence and complication rates associated with treatments for varicocele

Treatment	Refs.	Recurrence/ Persistence %	Overall complications	Specific Complications
Antegrade sclerotherapy	[1782, 1783]	5-9	Hydrocele (5.5%), haematoma, infection, scrotal pain, testicular atrophy, epididymitis	Technical failure 1-9%, left-flank erythema
Retrograde sclerotherapy	[1784, 1785]	6-9.8	Hydrocele (3.3%) wound infection, scrotal pain	Technical failure 6-7.5%, adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, venous perforation
Retrograde embolisation	[1784, 1786]	3-11	Hydrocele (10%) haematoma, wound infection	Technical failure 7-27%, pain due to thrombophlebitis, radiological complications (e.g., reaction to contrast media), misplacement or migration of coils (to femoral vein or right atrium), retroperitoneal haemorrhage, fibrosis, ureteric obstruction, venous perforation
Open operation				
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele	

Inguinal approach	[1787, 1788]	2.6-13	Hydrocele (7.3%), testicular atrophy, epididymo-orchitis, wound complications	Post-operative pain due to incision of external oblique fascia, genitofemoral nerve damage
Open retroperitoneal high ligation	[1776, 1789]	15-29	Hydrocele (5-10%), testicular atrophy, scrotal edema	External spermatic vein ligation failure
Microsurgical inguinal or subinguinal	[1777, 1787, 1790, 1791]	0.4	Hydrocele (0.44%), scrotal haematoma	
Laparoscopy	[1748, 1776, 1777, 1792, 1793]	3-6	Hydrocele (7-43%) epididymitis, wound infection, testicular atrophy due to injury of testicular artery, bleeding	External spermatic vein ligation failure, intestinal, vascular and nerve damage; pulmonary embolism; pneumo-scrotum; peritonitis; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumo-peritoneum)

10.4.3.5 Summary of evidence and recommendations for varicocele

Summary of evidence	**LE**
The presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment as the majority of boys with a varicocele will have no fertility problems later in life.	3
Varicocele repair may be effective in men with abnormal semen parameters, a clinical varicocele and otherwise unexplained male factor infertility.	1a
Although there are no prospective randomised studies evaluating this, meta-analyses have suggested that varicocele repair leads to sperm appearing in the ejaculate of men with non-obstructive azoospermia	2
Microscopic approach (inguinal/subinguinal) may have lower recurrence and complications rates than non-microscopic approaches (retroperitoneal and laparoscopic), although no RCTs are available yet.	2a
Varicocele is associated with raised DNA fragmentation and intervention has been shown to reduce DNA fragmentation.	2a

Recommendations	**Strength rating**
Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele.	Weak
Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation.	Weak

*10.4.4 **Male accessory gland infections and infertility***

10.4.4.1 Introduction

Infection of the male urogenital tract is a potentially curable cause of male infertility [1794-1796]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [1794]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [1797]. A systematic review of the relationship between sexually transmitted infections, such as those caused by *Chlamydia trachomatis*, genital mycoplasmas, *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and viruses, and infertility was unable to draw a strong association between sexually transmitted infections and male infertility due to the limited quality of reported data [1798].

10.4.4.2 Diagnostic evaluation

10.4.4.2.1 Semen analysis

Semen analysis (see Section 10.3.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. Leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CP/CPPS) (NIH IIa vs. NIH 3b National Institutes of Health classification for CP/CPPS).

10.4.4.2.2 Microbiological findings

After exclusion of UTI (including urethritis), > 10^6 peroxidase-positive white blood-cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In these cases, a semen culture or polymerase chain reaction (PCR) analysis should be performed for common urinary tract pathogens. A concentration of > 10^3 CFU/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia [1799]. The sampling should be delivered the same day to the laboratory because the sampling time can influence the rate of positive micro-organisms in semen and the frequency of isolation of different strains [1800]. The ideal diagnostic test for isolating *C. trachomatis* in semen has not yet been established [1801], but the most accurate method is PCR [1802-1804].

Historical data show that *Ureaplasma urealyticum* is pathogenic only in high concentrations (> 10^3 CFU/mL ejaculate). Fewer than 10% of samples analysed for Ureaplasma exceeded this concentration [1805]. Normal colonisation of the urethra hampers the significance of mycoplasma-associated urogenital infections, using samples such as the ejaculate [1806].

A meta-analysis indicated that *Ureaplasma parvum* and *Mycoplasma genitalium* were not associated with male infertility, but a significant relationship existed between *U. urealyticum* (OR: 3.03 95% CI: 1.02–8.99) and *Mycoplasma hominis* (OR: 2.8; 95% CI: 0.93– 3.64) [1807].

The prevalence of human papilloma virus (HPV) in the semen ranges from 2 to 31% in the general population and is higher in men with unexplained infertility (10-35.7%) [1808, 1809]. Recent systematic reviews have reported an association between male infertility, poorer pregnancy outcomes and semen HPV positivity [1810-1812]. However, data still needs to be prospectively validated to clearly define the clinical impact of HPV infection in semen. Additionally, seminal presence of Herpes Simplex virus (HSV)-2 in infertile men may be associated with lower sperm quality compared to that in HSV-negative infertile men [1797]. However, it is unclear if anti-viral therapy improves fertility rates in these men.

10.4.4.2.3 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [1813]. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections, and therefore cannot be considered a reliable indicator [1814]. According to the WHO classification, leukocytospermia is defined as > 10^6 WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [1815, 1816]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3b). Furthermore, leukocytospermia should be further confirmed by performing a peroxidase test on the semen. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms improves conception rates [1817].

10.4.4.2.4 Sperm quality

The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility and morphology has been demonstrated in a recent systematic review based on case-controlled studies [1818]. Both *C. trachomatis* and Ureoplasma spp. can cause decreased sperm density, motility, altered morphology and increased DNA damage. Data from a recent retrospective cross-sectional study showed that *U. urealyticum* was the most frequent single pathogen in semen of asymptomatic infertile men; a positive semen culture was both univariably ($p < 0.001$) and multi-variably ($p = 0.04$) associated with lower sperm concentration [1819]. Human papilloma virus can also induce changes in sperm density, motility and DNA damage [1808, 1809]. Mycoplasma spp. can cause decreased motility and development of antisperm antibodies [1797].

10.4.4.2.5 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [1796, 1820, 1821]. Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function through different pathways, but no correlations have been found [1822-1824].

The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process [1825]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion [1826].

10.4.4.2.6 Glandular secretory dysfunction

The secretory function of the prostate gland can be evaluated by measuring seminal plasma pH, citric acid, or γ-glutamine transpeptidase levels; the seminal plasma concentrations of these factors are usually altered during infection and inflammation. However, they are not recommended as diagnostic markers for MAGIs [1827].

Reactive oxygen species

Reactive oxygen species may be increased in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* infection, with subsequent decrease in ROS upon antibiotic treatment. However, the levels of ROS in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* in the semen are low, making it difficult to draw any firm conclusions [1828]. Chronic urogenital infections are also associated with increased leukocyte numbers [1829]. However, their biological significance in prostatitis remains unclear [1796].

10.4.4.2.7 Disease management

Treatment of CP/CPPS is usually targeted at relieving symptoms [1830, 1831]. The indications and aims of therapy are:

- reduction or eradication of micro-organisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters associated with fertility impairment [1832].

Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has provided symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [1832], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [1796, 1833].

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated with impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings [1828].

10.4.4.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men aged < 35 years, epididymitis is most often caused by *C. trachomati*s or *N. gonorrhoea* [1834, 1835]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTIs and occurs more often in men aged > 35 years [1836].

10.4.4.3.1 Diagnostic evaluation

10.4.4.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edn) criteria, may indicate persistent inflammatory activity. Transient reductions in sperm counts and progressive motility can be observed [1834, 1837, 1838]. Semen culture might help to identify pathogenic micro-organisms. Development of stenosis of the epididymal ducts, reduction of sperm count, and azoospermia are more important potential sequelae to consider in the follow-up of bilateral epididymitis (see Section 10.3.2).

10.4.4.3.1.2 Disease management

Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to also refer their sexual partners for evaluation and treatment [1839].

10.4.4.4 Summary of evidence and recommendation for male accessory gland infections

Summary of evidence	LE
Male accessory gland infections are not clearly associated with impaired natural conception.	3
Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical abnormalities.	2a
Although antibiotic treatment for MAGIs may result in improvement in sperm quality, it does not enhance the probability of conception.	2a

Recommendations	Strength rating
Treating male accessory gland infections may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	Weak
Data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia improve fertility outcomes.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

10.5 Non-Invasive Male Infertility Management

*10.5.1 **Idiopathic male infertility and oligo-astheno-terato-zoospermia***

Oligo-astheno-teratozoospermia (OAT) is a clinical condition with a reduced number of spermatozoa in the ejaculate, which is also characterised by reduced sperm motility and morphology; often referred to as OAT syndrome (OATS). Several conditions can cause OATS, although the aetiology may be unknown in a significant number of cases [96, 1665].

*10.5.2 **Empirical treatments***

10.5.2.1 Life-style

Studies suggest that environmental and lifestyle factors may contribute to idiopathic infertility acting additively on a susceptible genetic background [96, 1665]. Hence, lifestyle improvement can have a positive effect on sperm parameters (see below).

10.5.2.1.1 Weight loss

Few authors have investigated the role of weight loss on male fertility outcomes. Non-controlled studies have suggested that weight loss can result in improved sperm parameters [96, 1840, 1841]. However, data derived from RCTs are more conflicting. A meta-analysis of 28 cohort studies and 1,022 patients, documented that bariatric surgery did not improve sperm quality and function in morbidly obese men [1842]. Data on ART outcomes are lacking. However, it is important to recognise that weight loss can improve obesity-related secondary hypogonadism, which may result in better outcomes in couples seeking medical care for infertility, and is important for the general health of the male partner [1840, 1842].

10.5.2.1.2 Physical activity

Regular physical activity is recommended by the WHO in order to prevent and reduced the risk of several long-term chronic diseases [1843]. A recent meta-analysis has documented that moderate-intensity (20–40 metabolic equivalents [METs]/week) or even high-intensity (40–80 METs-h/week) recreational physical activity can result in better semen parameters [1844]. In addition, similar to what is observed from weight loss, improvements in hormonal profile have also been reported [1840].

10.5.2.1.3 Smoking

Epidemiological data indicates that about one in three men of reproductive age smokes, with the highest prevalence observed in Europe among all the WHO regions [1845]. Data derived from a large meta-analysis of 20 studies with 5,865 participants clearly show a negative association between smoking and sperm parameters [1845]. Experimental studies performed in rats have shown that nicotine has a dose-dependent deleterious effect on sperm, which can be improved by nicotine cessation [1846]. Data in men are lacking and only one case report has indicated an improvement of sperm parameters after 3 months of a smoking cessation programme [1847]. Similar data have been reported in a recent non-controlled study, which showed a possible benefit on ART after the male partner stopped smoking [1848].

10.5.2.1.4 Alcohol consumption

Data derived from a recent meta-analysis including 15 cross-sectional studies and 16,395 men suggested

that moderate alcohol does not adversely affect semen parameters, whereas high alcohol intake can have a detrimental effect on male fertility [1849]. Similar to what has been reported for weight loss; however, heavy chronic alcohol consumption (defined as > 2 drinks/day [1850]) can reduce testosterone levels, which can be restored by alcohol cessation [1851].

10.5.2.2 Antioxidant treatment

Inflammation is a positive reaction of the human body to overcome potential noxious stimuli. However, chronic inflammation can induce several negative biochemical and metabolic effects that contribute to the development of several medical conditions. Oxidative stress is considered to be of the most important contributing factors in the pathogenesis of idiopathic infertility. Reactive oxygen species, the final products of OS, can impair sperm function acting at several levels, including plasma membrane lipid peroxidation, which can affect sperm motility, the acrosome reaction and chromatin maturation leading to increased DNA fragmentation [1852]. Accordingly, seminal levels of ROS have been negatively associated with ART outcomes [1853]. Despite this, evidence for the role of antioxidant therapy in male infertility is still conflicting. A Cochrane systematic review and meta-analysis including 34 RCTs and 2,876 couples using various antioxidant compounds, it was concluded that antioxidant therapy had a positive impact on live-birth and pregnancy rates in sub-fertile couples undergoing ART cycles [1854]. Similar results were also reported in the most recent meta-analysis including 61 studies with 6,264 infertile men, aged 18-65 years [1855]. More recently, the Males, Antioxidants, and Infertility (MOXI) trial found that antioxidants did not improve semen parameters or DNA integrity compared to placebo among infertile men with male factor infertility. Moreover, cumulative live-birth rate did not differ at 6 months between the antioxidant and placebo groups (15% vs. 24%) [1856]. However, all the aforementioned studies also recognised important limitations: data were derived from low-quality RCTs with serious risk of bias due to poor methods of reporting randomisation; failure to report on the clinical outcomes including live-birth and clinical pregnancy rates; high attrition rates; and imprecision due to often low event rates and small overall sample sizes [1855]. No clear conclusions were possible regarding the specific antioxidants to use or and/or therapeutic regimes for improving sperm parameters and pregnancy rate [1855].

10.5.2.3 Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) have been advocated as a possible empirical treatment in male idiopathic infertility. The proposed mechanism of action is based on the activity of these compounds to block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion leading to an increase in pituitary gonadotropin release. The latter effect, by stimulating spermatogenesis, represents the rational basis for SERM administration to patients with reduced sperm count [1857]. In an initial meta-analysis including 11 RCTs, in which only 5 were placebo-controlled, it was concluded that SERMs were not associated with an increased pregnancy rate in the 459 patients analysed [1858]. In a subsequent Cochrane review published 1 year later, these findings were confirmed in a larger number of studies (n = 10 and 738 men), although positive effects on hormonal parameters were documented. More recently, Chua *et al.,* meta-analysed data derived from 11 RCTs and showed that SERMs were associated with a significantly increased pregnancy rate [1859]. Additionally, a significant improvement in sperm and hormonal parameters was detected. Similar results were confirmed in the latest updated meta-analysis of 16 studies [1857]. However, it should be recognised that the quality of the papers included was low and only a few studies were placebo-controlled. In conclusion, although some positive results relating to the use of SERMs in men with idiopathic infertility have been reported, no conclusive recommendations can be drawn due to poor quality of the available evidence. Furthermore, complications from the use of SERMs were under-reported.

10.5.2.4 Aromatase inhibitors

Aromatase, a cytochrome p450 enzyme, is present in the testes, prostate, brain, bone, and adipose tissue of men; it converts testosterone and androstenedione to oestradiol and oestrone, respectively. Oestradiol negatively feeds back on the hypothalamus and pituitary to reduce gonadotropic secretions, ultimately affecting spermatogenesis. In this context, aromatase inhibitors (AIs) may decrease oestrogen production by reversibly inhibiting cytochrome p450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex inhibiting the negative feedback of oestrogen on the hypothalamus resulting in stronger GnRH pulses that stimulate the pituitary to increase production of FSH [1860-1863]. Aromatase activity has been associated with male infertility characterised by testicular dysfunction with low serum testosterone and/or testosterone to oestradiol ratio. In this context, AIs have been reported to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility as an off-label option for treatment [1864]. Either steroidal (testolactone) and non-steroidal (anastrozole and letrozole) AIs significantly improve hormonal and semen parameters in infertile men, with a safe tolerability profile, although prospective RCTs are necessary to better define the efficacy of these medications in this clinical setting [1862, 1864].

Recommendations	Strength rating
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction can improve sperm quality and the chances of conception.	Weak
No clear recommendation can be made for treatment of patients with idiopathic infertility using antioxidants, although anti-oxidant use may improve semen parameters.	Weak
No conclusive recommendations on the use of selective oestrogen receptor modulators in men with idiopathic infertility can be drawn.	Weak
No conclusive recommendations on the use of either steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility can be drawn, even before testis surgery.	Weak

*10.5.3 **Hormonal therapy***

10.5.3.1 Gonadotrophins

Follicle Stimulating Hormone is primarily involved in the initiation of spermatogenesis and testicular growth during puberty. The role of FSH post puberty has not been clearly defined. Luteinising hormone stimulates testosterone production in the testes, but due to its short half-life, it is not suitable for clinical use. Human Chorionic Gonadotrophin acts in a similar manner to LH and can be used pharmacologically to stimulate testosterone release in men with failure of their hypothalamic-pituitary-gonadal axis. Human Chorionic Gonadotrophin can adequately stimulate spermatogenesis in men whom have developed hypopituitarism after normal puberty. Therefore, the treatment of men with secondary hypogonadism depends on whether or not they developed hypothalamic-pituitary failure before or after puberty [5].

10.5.3.2 Secondary hypogonadism

10.5.3.2.1 Pre-Pubertal-Onset

Congenital causes resulting in low gonadotropin production are associated with testicular size < 4 mL and/or cryptorchidism. Testes size of < 4 mL occurs when they have not been exposed to any gonadotropins at all. These conditions require combination therapy with both hCG and FSH with subcutaneous administration or GnRH by pulsed delivery using a subcutaneous pump [1865]. However, GnRH treatment requires a pulsatile secretion using specific devices for either intravenous or subcutaneous administration, which may limit patient compliance. Moreover, GnRH therapy should be limited to subjects with a residual pituitary gonadotropic activity [5].

As for the type of gonadotropin treatment, it is usual to commence hCG first and titrate the dose to achieve testosterone levels within the normal physiological range. However, FSH can be given first or in combination with hCG [125]. Human Chorionic Gonadotrophin is given twice weekly and in patients with congenital secondary hypogonadism in high dose, commencing at 1,000 IU twice weekly. Testosterone levels can be assayed every 2 weeks with dose increases until ideally mid-range testosterone is achieved. Dose increases can be to 2,000, 3,000, 4,000 and 5,000 IU two or three times a week, until normal testosterone levels are achieved [1866-1869]. Failure to achieve normal testosterone status at the high dose would indicate that primary testicular failure is present; probably as a result of cryptorchidism or failure of testicular development. Human Chorionic Gonadotrophin is also used to stimulate testicular descent into the scrotum in individuals with cryptorchidism. Once the hCG dose giving a normal level testosterone is established with the implication that intra-testicular testosterone has occurred, FSH 75-150 IU three times per week subcutaneously should be commenced. Usually the higher 150 IU dose three times weekly is needed to be successful in men with testicular volume < 4mL. The trophic response of the testes to FSH is variable in these patients and it may range from no effect to achieving testicular sizes of 12-15 mL [1870]. A trophic response is usually an indication of an increase in spermatogenesis. The production of new spermatogenesis may be evident after 3 months of FSH therapy, but could occur even after 18 months of treatment [1868-1870]. A low baseline sperm concentration does not indicate a poor response to gonadotropin therapy [1871]. Semen analysis can be assessed at 3-monthly intervals. These patients can be fertile with low sperm counts < 20 million/mL as there is a high proportion of motile sperm. Follicle-stimulating hormone therapy prior to GnRH is also effective in stimulating testicular growth and fertility in men with congenital hypogonadotropic hypogonadism (HH) [1872]. A larger initial testicular volume is the best prognostic factor for induction of successful spermatogenesis [1873].

10.5.3.2.2 Post-Pubertal Onset Secondary

If secondary hypogonadism develops after puberty, hCG alone is usually required first to stimulate spermatogenesis. Doses of subcutaneous hCG required may be lower than those used in individuals with pre-pubertal onset; therefore, a starting dose of 250 IU twice weekly is suggested, and if normal testosterone

levels are reached, hCG doses may be increased up to 2,000 IU twice weekly as for pre-pubertal onset. Again, semen analysis should be performed every 3 months to assess response, unless conception has taken place. If there is a failure of stimulation of spermatogenesis, then FSH can be added (75 IU three times per week, increasing to 150 IU three times per week if indicated). Similarly, combination therapy with FSH and hCG can be administered from the beginning of treatment, promoting better outcomes in men with HH [125]. No difference in outcomes were observed when urinary-derived, highly purified FSH was compared to recombinant FSH [125].

Greater baseline testicular volume is a good prognostic indicator for response to gonadotrophin treatment [1873]. Data had suggested that previous testosterone therapy can have a negative impact on gonadotropin treatment outcomes in men with HH [1873]. However, this observation has been subsequently refuted by a meta-analysis that did not confirm a real negative role of testosterone therapy in terms of future fertility in this specific setting [125].

In the presence of hyperprolactinaemia, causing suppression of gonadotrophins resulting in sub-fertility the treatment independent of aetiology (including a pituitary adenoma) is dopamine agonist therapy or withdrawal of the drug that causes the condition. Dopamine agonists used include bromocriptine, cabergoline and quinagolide.

10.5.3.3 Primary Hypogonadism

There is no substantial evidence that gonadotrophin therapy has any beneficial effect in the presence of classical testicular failure. Likewise, there are no data to support the use of other hormonal treatments (including SERMs or AIs) in the case of primary hypogonadism to improve spermatogenesis [97, 1874].

10.5.3.4 Idiopathic Male Factor Infertility

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 – 8 mIU/mL)[1875]. It has also been reported that FSH may improve sperm DNA fragmentation rates as well as ameliorating AMH and inhibin levels [1876-1879]. High-dose FSH therapy is more effective in achieving a testicular response than lower doses are [1880]. A Cochrane systematic review including six RCTs with 456 participants, different treatment protocols and follow-up periods concluded that FSH treatment resulted in higher live-birth and pregnancy rates compared with placebo or no treatment. However, no significant difference among groups was observed when ICSI or IUI were considered [1881]. In a more recent meta-analysis including 15 trials with > 1,200 patients, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies and pregnancies after ART [1882]. A further study showed that in azoospermic men undergoing TESE-ICSI there were improved SRRs and higher pregnancy and fertilisation rates in men treated with FSH compared to untreated men [1883]. In men with NOA, combination hCG/FSH therapy was shown to increase SRR in only one study [1884]. Human chorionic gonadotrophin alone prior to TESE in NOA has not been found to have any benefit on SRRs [1885]. Overall the evidence for the use of hormone therapy prior to SSR is limited and treatment should be confined to clinical trials and not used routinely in clinical practice.

10.5.3.5 Anabolic Steroid Abuse

Oligospermia or azoospermia as a result of anabolic abuse should be treated initially by withdrawal of the anabolic steroid. There is no common indication for treating this disorder; the management is based on case reports and clinical experience. Usually, adequate sperm numbers and quality will improve over a six to twelve month period. If after this interval the condition persists, then hCG without or in combination with FSH as an alternative to clomiphene can be used to try and stimulate spermatogenesis [1886].

10.5.3.6 Recommendations for treatment of male infertility with hormonal therapy

Recommendations	Strength rating
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH) (recombinant FSH; highly purified FSH) or pulsed Gonadotropin-releasing hormone (GnRH) via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong

The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given on the use of high-dose FSH in men with idiopathic infertility and prior (m)TESE and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong
Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
In the presence of hyperprolactinaemia, dopamine agonist therapy may improve spermatogenesis.	Weak

10.6 Invasive Male Infertility Management

*10.6.1 **Obstructive azoospermia***

Obstructive azoospermia (OA) is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction [1794]. Obstructive azoospermia is less common than NOA and occurs in 20-40% of men with azoospermia [1887, 1888]. Men with OA usually have normal FSH, testes of normal size and epididymal enlargement [1889]. Of clinical relevance, men with late maturation arrest may present with normal gonadotropins and testicular size and may be only distinguished from those with OA at the time of surgical exploration. The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

10.6.1.1 Classification of obstructive azoospermia

10.6.1.1.1 Intratesticular obstruction

Intratesticular obstruction occurs in 15% of men with OA [1890]. Congenital forms are less common than acquired forms (post-inflammatory or post-traumatic) (Table 43).

10.6.1.1.2 Epididymal obstruction

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men [1890-1893]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [1893]. Other congenital forms of epididymal obstruction include chronic sinu-pulmonary infections (Young's syndrome) [1894]. Acquired secondary to acute (e.g., gonococcal) and subclinical forms (e.g., Chlamydial) epididymitis are most commonly due to infections [1895, 1896]. Other causes may be trauma or surgical intervention [1897, 1898] (Table 43).

10.6.1.1.3 Vas deferens obstruction

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy [1895] (Table 42). Approximately 2-6% of these men request vasectomy reversal (see 2019 EAU Guidelines on Male Infertility). Vasal obstruction may also occur after hernia repair [1899, 1900]. The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [1584].

10.6.1.1.4 Ejaculatory duct obstruction

Ejaculatory duct obstruction is found in 1-5% of cases of OA and is classified as cystic or post-inflammatory or calculi of one or both ejaculatory ducts [1724, 1901] (Table 42). Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are typically midline. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst [1902], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [1903]. Paramedian or lateral intraprostatic cysts are rare [1904]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethra-prostatitis [1905]. Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low seminal volume, decreased or absent seminal fructose, and acidic pH. The seminal vesicles (anterior-posterior diameter > 15 mm) and ejaculatory duct (> 2.3 mm in width) are usually dilated [1901, 1905-1907].

10.6.1.1.4.1 Functional obstruction of the distal seminal ducts

Functional obstruction of the distal seminal ducts might be attributed to local neurogenic dysfunction [1908]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport can be observed as idiopathic or due to spinal cord injury, multiple sclerosis, retroperitoneal lymph node dissection, pelvic surgery, SSRIs, α-blockers and typical antipsychotic medications [1909].

Table 43: Causes of obstruction of the genitourinary system

Epididymis
Infection (acute/chronic epididymitis)
Trauma
Post-surgical iatrogenic obstruction (i.e., MESA, hydrocelectomy or other scrotal surgery)
Congenital epididymal obstruction (usually manifests as congenital bilateral absence of the vas deferens [CBAVD])
Other congenital forms of epididymal obstruction (Young's syndrome)
Vas deferens
Vasectomy
Vasotomy/vasography (with improper technique)
Post-surgical iatrogenic obstruction (i.e., scrotal surgery or herniorraphy)
Congenital unilateral (CUAVD) or bilateral absence of the vas deferens (CBAVD)
Ejaculatory ducts
Cysts (Mullerian utricular, prostatic or seminal vesicular)
Infection (acute/chronic epididymitis)
Traumatic
Postsurgical iatrogenic obstruction
Functional obstruction
Idiopathic/acquired local neurogenic dysfunction

10.6.1.2 Diagnostic evaluation

10.6.1.2.1 Clinical history

Clinical history-taking should follow the investigation and diagnostic evaluation of infertile men (See Section 10.3). Risk factors for obstruction include prior surgery, iatrogenic injury during inguinal herniorrhaphy, orchidopexy or hydrocelectomy.

10.6.1.2.2 Clinical examination

Clinical examination should follow the guidelines for the diagnostic evaluation of infertile men. Obstructive azoospermia is indicated by at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with:

- obstructive azoospermia and concomitant partial testicular failure;
- enlarged and dilated epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas deferens.

10.6.1.2.3 Semen analysis

Azoospermia means the inability to detect spermatozoa after centrifugation at ×400 magnification. At least two semen analyses must be carried out [1910, 1911] (see Section 10.3). When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in the semen pellet suggest complete seminal duct obstruction.

10.6.1.2.4 Hormone levels

Hormones including FSH and inhibin-B should be normal, but do not exclude other causes of testicular azoospermia (e.g., NOA). Although inhibin-B concentration is a good index of Sertoli cell integrity reflecting closely the state of spermatogenesis, its diagnostic value is no better than that of FSH and its use in clinical practice has not been widely advocated [1912].

10.6.1.2.5 Genetic testing

Inability to palpate one or both sides of the vas deferens should raise concern for a CFTR mutation. Any patient with unilateral or bilateral absence of the vas deferens or seminal vesicle agenesis should be offered CFTR testing [1913].

10.6.1.2.6 Testicular biopsy

Testicular biopsy must be combined with TESE for cryopreservation. Although studies suggest that a diagnostic or isolated testicular biopsy [1914] is the most important prognostic predictor of spermatogenesis and sperm retrieval, the Panel recommends not to perform testis biopsies (including fine needle aspiration

[FNA]) without performing simultaneously a therapeutic sperm retrieval, as this will require a further invasive procedure after biopsy. Furthermore, even patients with extremes of spermatogenic failure (e.g., Sertoli Cell Only syndrome [SCOS]) may harbour focal areas of spermatogenesis [1915, 1916].

10.6.1.3 Disease management

Sperm retrieval

10.6.1.3.1 Intratesticular obstruction

Only TESE allows sperm retrieval in these patients and is therefore recommended.

10.6.1.3.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [1917] is indicated in men with CBAVD. Testicular sperm extraction and percutaneous techniques, such as testicular sperm aspiration (TESA), are also options [1918]. The source of sperm used for ICSI in cases of OA and the aetiology of the obstruction do not affect the outcome in terms of fertilisation, pregnancy, or miscarriage rates [1919]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [1920] and it produces high pregnancy and fertilisation rates [1921]. In patients with OA due to acquired epididymal obstruction and with a female partner with good ovarian reserve, microsurgical epididymovasostomy (EV) is recommended [1922]. Epididymovasostomy can be performed with different techniques such as end-to-site and intussusception [1923].

Anatomical recanalisation following surgery may require 3-18 months. A recent systematic review indicated that the time to patency in EV varies between 2.8 to 6.6 months. Reports of late failure are heterogeneous and vary between 1 and 50% [1924]. Before microsurgery, and in all cases in which recanalisation is impossible, epididymal spermatozoa should be aspirated intra-operatively by MESA and cryopreserved to be used for subsequent ICSI procedures [1905]. Patency rates range between 65% and 85% and cumulative pregnancy rates between 21% and 44% [1898, 1925]. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings. Robot-assisted EV has similar success rates but larger studies are needed [1779].

10.6.1.3.3 Vas deferens obstruction after vasectomy

Vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. The mean post-procedural patency and pregnancy rates weighted by sample size were 90-97% and 52-73%, respectively [1898, 1925]. The average time to patency is 1.7-4.3 months and late failures are uncommon (0-12%) [1924]. Robot-assisted vasovasostomy has similar success rates, and larger studies, including cost-benefit analysis, are needed to establish its benefits over standard microsurgical procedures [1779].

The absence of spermatozoa in the intra-operative vas deferens fluid suggests the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas deferens has a thick “toothpaste” appearance; in this case microsurgical EV may be indicated [1926-1928]. Simultaneous sperm retrieval may be performed for future cryopreservation and use for ICSI; likewise, patients should be counselled appropriately.

10.6.1.3.4 Vas deferens obstruction at the inguinal level

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy. In these cases, TESE/MESA/PESA or proximal vas deferens sperm aspiration [1929] can be used for cryopreservation for future ICSI. Prostate cancer patients who express an interest in future fertility should be counselled for cryopreservation [1930, 1931].

10.6.1.3.5 Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction (EDO) depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) can be used in post-inflammatory obstruction and cystic obstruction [1901, 1905]. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision, unroofing or aspiration of the cyst is required [1901, 1905].

Intra-operative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the seminal vesicles (chromotubation) can help to confirm intra-operative opening of the ducts. Pregnancy rates after TURED are 20-25% [1724, 1901, 1932]. Complications following TURED include epididymitis, UTI, gross haematuria, haematospermia, azoospermia (in cases with partial distal ejaculatory duct obstruction) and urine reflux into the ejaculatory ducts and seminal vesicles [1901].

Alternative therapies for EDO include, seminal vesiculoscopy to remove debris or calculi and balloon dilation and laser incision for calcification on TRUS [1933]. The alternatives to TURED are MESA, PESA, TESE, proximal vas deferens sperm aspiration and seminal vesicle-ultrasonically guided aspiration.

10.6.1.4 Summary of evidence and recommendations for obstructive azoospermia

Summary of evidence	LE
Obstructive lesions of the seminal tract are frequent in azoospermic or severely oligozoospermic patients, usually with normal-sized testes and normal reproductive hormones.	3

Recommendations	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA and TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong

*10.6.2 **Non-obstructive azoospermia***

Non-obstructive azoospermia (NOA) is defined as the absence of sperm at the semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed at least at two consecutives semen analyses [1522]. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

10.6.2.1 Investigation of non-obstructive azoospermia

The diagnosis of NOA is based on the evidence of two consecutive semen analyses confirming azoospermia. Causes of OA should be ruled out. Patients with NOA should undergo a comprehensive assessment to identify genetically transmissible conditions, potential treatable causes of azoospermia, and potential health-relevant co-morbidity (e.g., testicular cancer and hypogonadism [of any type]). A detailed medical history (e.g., history of cryptorchidism, previous gonadotoxic treatments for cancer, etc.) and socio-demographic characteristics [1934], along with a comprehensive physical examination should be performed in every patient to detect conditions potentially leading to azoospermia, while ruling out co-morbidity frequently associated with azoospermia. Non-obstructive azoospermia can be the first sign of pituitary or germ cell tumours of the testis [1935-1937]. Patients with NOA have been shown to be at increased risk of being diagnosed with cancer [1938]. Moreover, other systemic conditions such as MetS, T2DM, osteoporosis and CVDs have been more frequently observed in patients with NOA compared to normozoospermic men [1939-1941]. Azoospermic men are at higher risk of mortality [1942, 1943]. Therefore, investigation of infertile men provides an opportunity for long-term risk stratification for other co-morbid conditions [1944].

Genetic tests should be performed in patients with NOA to detect genetic abnormalities. As discussed (see Section 10.3), patients should undergo karyotype analysis [1544, 1545], along with a screening of Y-chromosome micro-deletions [1595, 1945] and of the gene coding for CFTR in order to exclude concomitant mutations, and to rule out CBAVD [1579, 1580]. Genetic counselling for eventual transmissible and health-relevant genetic conditions should be provided to couples.

All patients should undergo a complete hormonal investigation to exclude concomitant hypogonadism, which has been found in about 30% of patients with NOA [389, 1946, 1947]. A correct definition of the type of the associated hypogonadism (i.e., hypogonadotropic hypogonadism vs. hypergonadotropic vs. compensated hypogonadism) is relevant to differentiate diagnostic and therapeutic approaches to the patient [1948].

Scrotal US may show signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and/or microcalcifications) and testicular tumours. Testicular volume may be a predictor of spermatogenic function [1516] and is usually, but not invariably, low in patients with NOA. Some authors have advocated that testicular perfusion detected at US Doppler assessment can predict surgical sperm retrieval at TESE and guide testicular biopsies [1949]; however, to date, data are inconsistent to suggest a routine role of testicular Doppler evaluation before TESE. In a recent multicentre study including 806 men submitted to mTESE, the

size of seminiferous tubules assessed with pre-operative US was significantly associated with sperm retrieval outcomes, with a sensitivity and specificity of 76.7% and 80.7% for a cut-off point of 250 µm, respectively [1950].

10.6.2.2 Surgery for non-obstructive azoospermia

Surgical treatment for NOA is mostly aimed at retrieval of vital sperm directly from the testes (either uni- or bilaterally). This treatment is normally part of ART protocols, including IVF cycles via ICSI. Techniques and indications for surgical sperm retrieval in patients with NOA are discussed below. Any surgical approach aimed at sperm retrieval must be considered not a routine and simple biopsy; in this context, performing a diagnostic biopsy before surgery (any type) unless dedicated to ART protocols is currently considered inappropriate.

10.6.2.3 Indications and techniques of sperm retrieval

Spermatogenesis within the testes may be focal, which means that spermatozoa can usually be found in small and isolated foci. With a wide variability among cohorts and techniques, positive SRRs have been reported in up to 50% of patients with NOA [1951, 1952]. Numerous predictive factors for positive sperm retrieval have been investigated, although no definitive factors have been demonstrated to predict sperm retrieval [1952].

Historically, there is a good correlation between the histology found at testicular biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval [1914, 1953, 1954]. The presence of hypospermatogenesis at testicular biopsy showed good accuracy in predicting positive sperm retrieval after either single or multiple conventional TESE or mTESE compared with maturation arrest pattern or SCOS [1914, 1953, 1954]. However, formal diagnostic biopsy is not recommended in this clinical setting for the reasons outlined above.

Hormonal levels, including FSH, LH, inhibin B and AMH have been variably correlated with sperm retrieval outcomes at surgery, and data from retrospective series are still controversial [1883, 1955-1960]. Similarly, conflicting results have been published regarding testicular volume as a predictor of positive sperm retrieval [1883, 1914, 1958]. Therefore, no clinical variable may be currently considered as a reliable predictor for positive sperm retrieval throughout ART patient work-up [1952].

In case of complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is zero and therefore TESE procedures are contraindicated [1600]. Conversely, patients with Klinefelter syndrome [1562] and a history of undescended testes have been shown to have higher chance of finding sperm at surgery [1958].

Historically, surgical techniques for retrieving sperm in men with NOA include testicular sperm aspiration (TESA), single or multiple conventional TESE (cTESE) and mTESE.

- **Fine needle aspiration mapping**

Fine needle aspiration (FNA) mapping technique has been proposed as a prognostic procedure aimed to select patients with NOA for TESE and ICSI [1961]. The procedure is performed under local anaesthesia in the office and percutaneous aspiration is performed with 23G needle in multiple sites, ranging from 4 to 18 [1961]. The retrieved tissue is sent for cytological and histological evaluation to provide information on the presence of mature sperm and on testicular histological pattern. Given that focal spermatogenesis may occur within the testes of patients with NOA, FNA mapping may provide information on the sites with the higher probability of retrieving sperm, thus serving as a guide for further sperm retrieval surgery in the context of ART procedures (e.g., ICSI). Turek *et al.* have shown that a higher number of aspiration sites may increase the chance of finding sperm [1962, 1963]. The extent and type of subsequent sperm retrieval procedure can be tailored according to the FNA mapping results: TESA or TESE could be suggested in case of multiple positive sites for sperm, while a more precise and potentially more-invasive technique, such as mTESE, could be considered for patients with few positive sites at FNA [1961]. However, no RCTs have compared the diagnostic yield from FNA and mTESE. A positive FNA requires a secondary therapeutic surgical approach, which may increase the risk of testicular damage, and without appropriate cost-benefit analysis, is not justifiable. No studies have evaluated the salvage rate of mTESE in men who have undergone FNA mapping. Therefore, FNA mapping cannot be recommended as a primary therapeutic intervention in men with NOA until further RCTs are undertaken.

- **Testicular sperm aspiration**

Testicular sperm aspiration (TESA) is a minimally invasive, office-based, procedure in which testicular tissue is retrieved with a biopsy needle under local anaesthesia. Reported SRRs with TESA range from 11 to 60% according to patient profile and surgical techniques [1964-1967]. Data have shown that using larger needles (18-21G) with multiple passes could yield a higher chance of positive sperm retrieval [1967]. Complications

after TESA are uncommon and mainly include minor bleeding with scrotal haematoma and post-operative pain [1967].

As a less-invasive and less-costly procedure TESA has been proposed as a possible first-line approach before sending patients for a more-invasive procedure [1967]. To date no RCTs have compared SRRs from TESA, cTESE and mTESE. A meta-analysis including data from case-control studies, reported that TESE was two times (95% CI: 1.8-2.2) more likely to result in successful sperm retrieval as compared with TESA [1952]. Given the low success rates compared with TESE, TESA is no longer recommended in men with NOA.

- **Conventional and microTESE**

In patients with NOA, a testicular sperm extraction procedure is required to retrieve sperm that can be utilised in ARTs. Testicular sperm extraction was first performed through a single or multiple open biopsy of the testicle (conventional TESE [cTESE]). Conventional TESE requires a scrotal incision and open biopsy of the testes [1968]. Reported SRRs in single-arm studies are about 50% [1951]. Observational studies have demonstrated that multiple biopsies yield a higher chance of sperm retrieval [1951, 1969].

In 1999, Schlegel pioneered the use of a micro testicular extraction of sperm (mTESE) approach, which utilised an operative optical microscope to inspect seminiferous tubules at a magnification of 20-25x and extract those tubules which were larger, dilated and opaque as these were more likely to harbor sperm [1968]. The rationale of this technique is to increase the probability of retrieving sperm with a lower amount of tissue sampled and a subsequent lower risk of complications. A meta-analysis that pooled data analysis of case-control studies comparing cTESE with mTESE showed a lower unadjusted SRR of 35% (95% CI: 30-40) for cTESE and 52% for mTESE [1952]. A more recent meta-analysis comparing cTESE and mTESE in patients with NOA showed a mean SRR of 47% (95% CI: 45;49%). No differences were observed when mTESE was compared with cTESE (46 [range 43-49] % for cTESE vs. 46 [range 42-49] % for mTESE, respectively) [1970].

Meta-regression analysis demonstrated that the SRR per cycle was independent of age and hormonal parameters at enrolment. However, the SRR increased as a function of testicular volume. Retrieved sperms resulted in a live-birth rate of up to 28% per ICSI cycle [1912]. The difference in surgical sperm retrieval outcomes between the two meta-analyses may be explained by the data studied [1952] only one analysed case control studies whilst Corona *et al.* [1912] also included the single randomised controlled trial), but it is important to note that all the studies comparing cTESE and mTESE have shown that the latter is superior in retrieving sperm.

The probability of finding vital sperm at TESE varies also according to testicular histology: data from non-randomised studies comparing cTESE with mTESE have shown a higher chance of sperm retrieval with mTESE only for patients with a histological diagnosis of SCOS [1971]. In such cases, results ranged from 22.5 to 41% and from 6.3 to 29% for mTESE vs. cTESE, respectively [1971]. Conversely, no difference between the two techniques has been found when comparing patients with a histology suggestive of maturation arrest [1971]. A single study showed a small advantage of mTESE when hypospermatogenesis was found [1972]. In light of these findings, some authors have advocated that cTESE could be the technique of choice in patients with a histological finding of maturation arrest or hypo-spermatogenesis [1952, 1971].

In a study assessing the role of salvage mTESE after a previously failed cTESE or TESA, sperm were successfully retrieved in 46.5% of cases [1857]. In studies reporting sperm retrieval by micro-TESE for men who had failed percutaneous testicular sperm aspiration or non-microsurgical testicular sperm extraction, the SRR was 39.1% (range 18.4-57.1%) [1973, 1974]. Similarly, a variable SRR has been reported for salvage mTESE after a previously failed mTESE (ranging from 18.4% to 42.8%) [1975, 1976].

Conventional TESE has been associated with a higher rate of complications compared with other techniques [1951]. A total of 51.7% of patients have been found with intratesticular haematoma at scrotal US 3 months after surgery, with testicular fibrosis observed in up to 30% of patients at 6-months' assessment [1977].

A recent meta-analysis investigated the risk of hypogonadism after TESE due to testicular atrophy [1978]; patients with NOA experienced a mean 2.7 nmol/L decrease in total testosterone 6 months after cTESE, which recovered to baseline within 18-26 months. Lower rates of complications have been observed with mTESE compared to cTESE, both in terms of haematoma and fibrosis [1971]. Both procedures have shown a recovery of baseline testosterone levels after long-term follow-up [1972, 1979].

- **Follow-up after TESE**

When compared with cTESE, mTESE has been reported to have fewer post-operative complications and negative effects on testicular function. In a recent meta-analysis analysing the complications of TESE, men with Klinefelter syndrome and NOA had the largest decrease in total testosterone levels 6 months after TESE (mean decrease of 4.1 and 2.7 nmol/L, respectively), which recovered to baseline levels 26 and 18 months after TESE, respectively [1978, 1979]. Therefore, it would be reasonable to provide long-term endocrinological follow-up after TESE (any type) to detect hypogonadism, particularly for patients with Klinefelter syndrome. Testosterone measurement could be offered in asymptomatic men at 18 months post-TESE or in those men who become symptomatic for hypogonadism after surgery [1980]. Temporary discontinuation of treatment may reveal the expected recovery of testosterone secretion and revise the decision for testosterone therapy [1981]. Human chorionic gonadotropin or selective oestrogen receptors modulators (SERMs) administration could be considered in highly selected, hypogonadal patients who have not completed their fertility attempts to increase intratesticular testosterone concentration and manage the hypogonadal symptoms [1979].

The main limitation to contemporary literature is the paucity of randomised controlled studies comparing cTESE and mTESE. Although no difference in SSR was observed between cTESE/mTESE techniques in patients with NOA in the latest and most comprehensive meta-analysis [1970], it is important to note that in all the individual trials comparing cTESE and mTESE the latter was superior in retrieving sperm. Furthermore, the current data suggests that mTESE has less complications than cTESE and therefore the consensus opinion of the guidelines panel is that mTESE is the optimum approach for surgical sperm retrieval procedures. However, this is based on low-quality evidence and larger RCTs comparing SSR, risks and costs between the two techniques are urgently needed.

- **Hormonal therapy prior to surgical sperm retrieval approaches**

Stimulating spermatogenesis by optimising intratesticular testosterone (ITT) has been proposed to increase the chance of sperm retrieval at the time of surgery in men with NOA. Similarly, increasing FSH serum levels could stimulate spermatogenesis. There is evidence that treatment with hCG can lead to an increase in ITT [1878] and Leydig cells within the testes [1982]. It has been shown in azoospermic patients with elevated gonadotropins levels that administration of hCG and/or FSH can lead to a so-called “gonadotropins reset”, with a reduction in FSH plasma concentrations and improvement in Sertoli cells function [1983]. Similarly, clomiphene citrate may increase pituitary secretion by blocking feedback inhibition of oestradiol, thus inducing an increase in FSH and LH in patients with NOA [1984]. While azoospermic patients with secondary hypogonadism should be treated accordingly to stimulate sperm production [389], no RCT has shown a benefit of hormonal treatment to enhance the chances of sperm retrieval among patients with idiopathic NOA [1985]. In a large multicentre case-control study, 496 patients with idiopathic NOA treated with a combination of clomiphene, hCG and human menopausal gonadotropin according to hormonal profile, were compared with 116 controls subjected to mTESE without receiving any pre-operative treatment [1884]. A total of 11% of treated patients had sperm in the ejaculate at the end of treatment; of the remaining patients, 57% had positive sperm retrieval at mTESE as compared with 33% in the control group. Likewise, in a small case-control study including 50 men with idiopathic NOA, of whom 25 were treated with recombinant FSH before mTESE, there was observed a 24% SRR compared with 12% in the control group [1883]. Conversely, Gul *et al.* [1885] failed to find any advantage of pre-operative treatment with hCG compared with no treatment, in 34 idiopathic NOA patients candidates for mTESE.

Hormonal therapy has been proposed to increase the chance of sperm retrieval at salvage surgery after previously failed cTESE or mTESE. Retrospective data have shown that treatment with hCG and recombinant FSH could lead to a 10-15% SRR at salvage mTESE [1878, 1986]. In a small case-control study 28 NOA patients were treated with hCG with or without FSH for 4-5 months before salvage mTESE and compared with 20 controls subjected to salvage surgery [1987]. Sperm retrieval rate was 21% in the treated group compared with 0% in the control group. The histological finding of hypo-spermatogenesis emerged as a predictor of sperm retrieval at salvage surgery after hormonal treatment [1987]. Further prospective trials are needed to elucidate the effect of hormonal treatment before salvage surgery in NOA patients, with a previously failed cTESE or mTESE. However, patients should be counselled that the evidence for the role of hormone stimulation prior to sperm retrieval surgery in men with idiopathic NOA is limited [1988]. Currently, it is not recommended in routine practice.

10.6.2.4 Recommendations for Non-Obstructive Azoospermia

Recommendations	Strength rating
Patients with non-obstructive azoospermia (NOA) should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated co-morbidity. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.	Strong
Surgery for sperm retrieval can be performed in men who are candidates for assisted reproductive technology (i.e., ICSI). In patients with complete AZFa and AZFb microdeletions, surgery is contraindicated since the chance of sperm retrieval is zero.	Strong
Fine needle aspiration and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to cTESE and mTESE.	Weak
Fine needle aspiration mapping as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Microdissection TESE is the technique of choice for retrieving sperm in patients with NOA.	Weak
No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.	Weak
No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone [FSH]); highly purified FSH; human chorionic gonadotrophin; aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE.	Weak

10.7 Assisted Reproductive Technologies

*10.7.1 **Types of assisted reproductive technology***

Assisted reproductive technology consists of procedures that involve the *in vitro* handling of both human oocytes and sperm, or of embryos, with the objective of establishing pregnancy [1989, 1990].

Once couples have been prepared for treatment, the following are the steps that make up an ART cycle:

1. Pharmacological stimulation of growth of multiple ovarian follicles, while at the same time other medications is given to suppress the natural menstrual cycle and down-regulate the pituitary gland.
2. Careful monitoring at intervals to assess the growth of the follicles.
3. Ovulation triggering: when the follicles have reached an appropriate size, a drug is administered to bring about final maturation of the eggs.
4. Egg collection (usually with a trans-vaginal US probe to guide the pickup) and, in some cases of male infertility, sperm retrieval.
5. Fertilisation process, which is usually completed by IVF or ICSI.
6. Laboratory procedures follow for embryo culture: culture media, oxygen concentration, co-culture, assisted hatching etc.
7. The embryos are placed into the uterus. Issues of importance here include endometrial preparation, the best timing for embryo transfer, how many embryos to transfer, what type of catheter to use, the use of US guidance, need for bed rest etc.
8. Luteal phase support, for which several hormonal options are available.

Fertility treatments are complex and each cycle consists of several steps. If one of the steps is incorrectly applied, conception may not occur [1989].

Several ART techniques are available:

10.7.1.1 Intra-uterine insemination (IUI)

Intra-uterine insemination is an infertility treatment that involves the placement of the prepared sperm into the uterine cavity timed around ovulation. This can be done in combination with ovarian stimulation or in a natural cycle. The aim of the stimulation cycle is to increase the number of follicles available for fertilisation and to enhance the accurate timing of insemination in comparison to the natural cycle IUI [1991-1993].

Intra-uterine insemination is generally, though not exclusively, used when there is at least one patent fallopian tube with normal sperm parameters and regular ovulatory cycles (unstimulated cycles) and when the female partner is aged < 40 years.

The global pregnancy rate (PR) and delivery rate (DR) for each IUI cycle with the partner's sperm are 12.0% and 8.0%, respectively. Using donor sperm, the resultant PR and DR per cycle are 17.0% and 12.3%, respectively [1994]. The rates of successful treatment cycles for patients decrease with increase in age, and the birth rates across all age groups have remained broadly stable over time. The highest birth rates have been reported in patients younger than 38 years (14% in patients aged < 35 years and 12% in those aged 35-37 years). The rates of successful treatment are low for patients older than 42 years. The multiple pregnancy rate (MPR) for IUI is ~8% [1992]. Intra-uterine insemination is not recommended in couples with unexplained infertility, male factor infertility and mild endometriosis, unless the couples have religious, cultural or social objections to proceed with IVF [1995].

Intra-uterine insemination with ovarian stimulation is a safer, cheaper, more patient-friendly and non-inferior alternative to IVF in the management of couples with unexplained and mild male factor infertility [1991, 1992]. A recent RCT showed lower multiple pregnancy rates and comparable live-birth rates in patients treated with IUI with hormonal stimulation when compared to women undergoing IVF with single embryo transfer [1996]. Additionally, IUI is a more cost-effective treatment than IVF for couples with unexplained or mild male subfertility [1997].

10.7.1.2 In vitro fertilisation (IVF)

Involves using controlled ovarian hyperstimulation to recruit multiple oocytes during each cycle from the female partner. Follicular development is monitored ultrasonically, and ova are harvested before ovulation with the use of US-guided needle aspiration. The recovered oocytes are mixed with processed semen to perform IVF. The developing embryos are incubated for 2-3 days in culture and then placed trans-cervically into the uterus.

The rapid refinement of embryo cryopreservation methods has resulted in better perinatal outcomes of frozen-thawed embryo transfer (FET) and makes it a viable alternative to fresh embryo transfer (ET) [1998, 1999]. Frozen-thawed embryo transfer seems to be associated with lower risk of gestational complications than fresh ET. Individual approaches remain appropriate to balance the options of FET or fresh ET at present [2000].

Generally, only 20%-30% of transferred embryos result in clinical pregnancies. The global PR and DR per aspiration for non-donor IVF is 24.0% and 17.6%, respectively [1994].

According to the NICE guidelines, IVF treatment is appropriate in cases of unexplained infertility for women who have not conceived after 2 years of regular unprotected sexual intercourse [2001].

10.7.1.3 Intracytoplasmic sperm injection

Intracytoplasmic sperm injection is a procedure through which a single sperm is injected directly into an egg using a glass micropipette.

The difference between ICSI and IVF is the method used to achieve fertilisation. In conventional IVF, oocytes are incubated with sperm in a Petri dish, and the male gamete fertilises the oocyte naturally. In ICSI, the cumulus–oocyte complexes go through a denudation process in which the cumulus oophorus and corona radiata cells are removed mechanically or by an enzymatic process. This step is essential to enable microscopic evaluation of the oocyte regarding its maturity stage, as ICSI is performed only in metaphase II oocytes [2002]. A thin and delicate glass micropipette (injection needle) is used to immobilise and pick up morphologically normal sperm selected for injection. A single spermatozoon is aspirated by its tail into the injection needle, which is inserted through the zona pellucida into the oocyte cytoplasm. The spermatozoon is released at a cytoplasmic site sufficiently distant from the first polar body. During this process, the oocyte is held still by a glass micropipette [2002].

With this technique the oocyte can be fertilised independently of the morphology and/or motility of the spermatozoon injected.

Intracytoplasmic sperm injection is currently the most commonly used ART, accounting for 70–80% of the cycles performed [2003].

The procedure was first used in cases of fertilisation failure after standard IVF or when an inadequate number of sperm cells was available. The consistency of fertilisation independent of the functional quality of the

spermatozoa has extended the application of ICSI to immature spermatozoa retrieved surgically from the epididymis and testis [2004]. Intracytoplasmic sperm injection is the natural treatment for couples with severe male factor infertility and is also used for a number of non-male factor indications (Table 44) [2005].

The need to denude the oocyte allows assessment of the nuclear maturity of the oocyte. Intracytoplasmic sperm injection is also preferred in conjunction with pre-implantation genetic diagnosis and has recently been used to treat HIV discordant couples, in whom there is a pressing need to minimise exposure of the oocyte to a large number of spermatozoa [2004].

The global PR and DR per aspiration for ICSI is 26.2% and 19.0%, respectively [1994]. For all ages and with all the different sperm types used, fertilisation after ICSI is at approximately 70%-80% and it ensures a clinical pregnancy rate of up to 45% [2003, 2004].

Existing evidence does not support ICSI in preference over IVF in the general non-male factor ART population; however, in couples with unexplained infertility, ICSI is associated with lower fertilisation failure rates than IVF [2005].

Overall, pregnancy outcomes from ICSI are comparable between epididymal and testicular sperm and also between fresh and frozen–thawed epididymal sperm in men with OA [2006]. However, these results are from studies of low evidence [2005].

Sperm injection outcomes with fresh or frozen–thawed testicular sperm have been compared in men with NOA. In a meta-analysis of 11 studies and 574 ICSI cycles, no significant difference was observed between fresh and frozen–thawed testicular sperm with regards to fertilisation rate (RR: 0.97, 95% CI: 0.92–1.02) and clinical pregnancy rates (RR: 1.00, 95% CI: 0.75–1.33) [2007]. However, no meta-analysis was performed on data regarding implantation, miscarriage, and low-birth rates.

10.7.1.4 Testicular sperm in men with raised DNA fragmentation in ejaculated sperm

The use of testicular sperm for ICSI is associated with possibly improved outcomes compared with ejaculated sperm in men with high sperm DNA fragmentation [1535, 2005]. Men with unexplained infertility with raised DNA fragmentation may be considered for TESE after failure of ART, although they should be counselled that live-birth rates are under reported in the literature and patients must weigh up the risks of performing an invasive procedure in a potentially normozoospermic or unexplained condition. The advantages of the use of testicular sperm in men with cryptozoospermia have not yet been confirmed in large scale randomised studies [2008].

In terms of a practical approach, urologists may offer the use of testicular sperm in patients with high DNA fragmentation. However, patients should be counselled regarding the low levels of evidence for this (i.e., non-randomised studies). Furthermore, testicular sperm should only be used in this setting once the common causes of oxidative stress have been excluded including varicoceles, modifications of dietary/lifestyle factors and treatment of accessory gland infections.

Table 44: Fertilisation methods for male-factor and non-male factor infertility (adapted from [2005]**)**

	Fertilisation method
Male Factor Infertility	
Sperm derived from men with azoospermia	ICSI mandatory
Severe OAT	ICSI highly recommended
Moderate OAT	IVF and ICSI equally effective
Isolated teratozoospermia	IVF and ICSI equally effective
Absolute asthenozoospermia	ICSI mandatory
Globozoospermia	ICSI mandatory
Anti-sperm antibodies	IVF and ICSI equally effective
Sperm DNA fragmentation	ICSI recommended

Non-male factor infertility	
Unexplained infertility	Equally effective. Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. It should be noted for clarification that in the absence of male factors, ICSI should not be offered in the first treatment cycle [2009].
General non-male factor population	Equally effective, slightly in favour of IVF
Poor quality oocytes and advanced maternal age	Equally effective, slightly in favour of IVF
Pre-implantation genetic testing	ICSI highly recommended
Poor responders	Equally effective, slightly in favour of IVF
Tubal ligation	IVF preferable
Sero-discordant couples	Equally effective

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; OAT = oligo-asthenoter-atozoospermia

Intracytoplasmic sperm injection is carried out using viable sperm populations. Several semen processing techniques have been developed to select the optimal sperm fraction for ICSI. Density gradient centrifugation (DGC) and the swim-up procedures have been used as standards for semen preparation for ICSI for more than two decades [2010]. However, these traditional sperm selection techniques are unable to select sperm fractions with optimal DNA integrity and functional characteristics. Advanced sperm selection techniques have been introduced to optimise the selection of high-quality sperm for ICSI [2011]. These selection methods are based on sperm surface charge (electrophoresis and zeta potential), apoptosis (magnetic-activated sperm cell sorting (MACS) and glass wool), membrane maturity (hyaluronic acid binding), or ultra-morphological sperm assessment [2012].

10.7.1.4 Intra-cytoplasmic morphologically selected sperm injection

Intra-cytoplasmic morphologically selected sperm injection (IMSI) was first introduced in 2002 as a modification of the ICSI technique [2013]. This technique increases the magnification of sperm to > 6,000 times; the purpose of which is to perform the motile sperm organelle morphology examination (MSOME), a method used to select spermatozoa that have the choicest morphology in couples with the most severe male factor. Bartoov *et al.* showed that, for patients with a history of ICSI failure, addition of IMSI resulted in a 60% pregnancy rate, compared with a 30% rate for patients not using IMSI [2014]. The pregnancy rate following IVF-IMSI was significantly higher and the miscarriage rate significantly lower, than for the routine IVF-ICSI procedure (60.0% vs. 25.0%, and 14% vs. 40%, respectively) [2015]. However, the most recently updated Cochrane review neither supported nor refuted the clinical use of IMSI [2016].

10.7.1.5 Physiological ICSI (PICSI) technique: a selection based on membrane maturity of sperm

The Human oocytes are surrounded by hyaluronic acid (HA), which acts as a natural selector. Only mature sperm that express receptors specific to HA can reach the oocytes and fertilise them. Those sperm have normal shapes, low DNA fragmentation rates, and low frequency of chromosomal aneuploidy [2017]. Several studies have attempted to verify whether sperm selection based on HA binding affects IVF outcomes. A meta-analysis included six prospective randomised studies and one retrospective study, all of which used a PICSI sperm-selection dish (a plastic culture dish with microdots of HA hydro gel on its inner surface) or the Sperm Slow method (a viscous medium containing HA). No improvements in fertilisation and pregnancy rates were recorded, although embryo quality was superior in PICSI compared with conventional ICSI [2017]. A recent large-sample multicentre randomised trial provided conclusive evidence against the use of PICSI in ART (PICSI live-birth rate vs. ICSI: OR: 1.12, 95% CI: 0.95–1.34) [2018]. A time-lapse study found no difference in embryo development dynamics in oocytes fertilised via HA-ICSI vs. conventional ICSI [2019].

10.7.1.6 Magnetic-activated cell sorting

Magnetic-activated cell sorting (MACS) is an advanced sperm-selection technique used to isolate sperm that do not show signs of apoptosis and, therefore, are presumed to have a lower rate of DNA damage [2011]. Use of MACS after density gradient centrifugation (DGC) has been found to improve sperm morphology and decrease DNA fragmentation and apoptotic markers, but it reduces motility of the selected sperm [2011, 2012]. Magnetic-activated cell sorting failed to improve ICSI outcomes compared with DGC or swim-up, although a slightly higher pregnancy rate (RR: 1.5, 95% CI: 1.14–1.98) was observed in MACS patients relative to the control group [2020]. No difference in implantation or miscarriage rate was noted (RR: 1.03, 95% CI: 0.8–1.31 and RR: 2, 95% CI: 0.19–20.9, respectively).

Finally, another RCT performed on infants conceived via ovum-donation IVF cycles did not report any differences in terms of obstetrical and perinatal outcomes between pregnancies or babies conceived with sperm selected via MACS or swim-up [2021].

*10.7.2 **Safety***

The most significant risk of pre-implantation ART treatment is the ovarian hyperstimulation syndrome, a potentially life-threatening condition resulting from excessive ovarian stimulation during ART techniques, ranging from 0.6% to 5% in ART cycles [2022].

Other problems include the risk of multiple pregnancies due to the transfer of more than one embryo and the associated risks to mother and baby, including multiple and preterm birth. The most prevalent maternal complications include pre-eclampsia, gestational diabetes, placenta previa, placental abruption, postpartum haemorrhage, and preterm labour and delivery [1956, 2023, 2024]. The risks of foetal demise during the third trimester, perinatal mortality, preterm birth, and low birth weight increase with the number of foetuses in the pregnancy. The foetal consequences of preterm birth (cerebral palsy, retinopathy, and broncho-pulmonary dysplasia) and foetal growth restriction (polycythaemia, hypoglycaemia, and necrotising enterocolitis) are significant [2025].

The average number of embryos transferred in fresh non-donor IVF and ICSI cycles in 2011 was 1.91, compared with 2.09 in 2008, 2.00 in 2009, and 1.95 in 2010, reflecting a continuing decrease from previous years. The average number of embryos transferred in frozen ET cycles decreased from 1.72 in 2008 to 1.65 in 2009 to 1.60 in 2010 and to 1.59 in 2011 [2026].

The global multiple birth rate for fresh cycle transfer has decreased from 21.5% in 2010 to 20.5% in 2011 and for frozen ET cycles from 12.0% to 11.5% [1994].

In 2011, the rate of early pregnancy loss was 20.1% after fresh ET, compared with 25.4% after frozen ET. Both rates showed wide regional variation [1994]. The multiple birth rates after fresh non-donor ET was 19.6% (twins) and 0.9% (triplets and higher-order births); for frozen ET non-donor cycles, twin and triplet and higher-order birth rates were 11.1% and 0.4%, respectively [1994].

Rates of premature delivery and perinatal mortality were lower for frozen ETs than for fresh ETs. The global preterm DR after non-donor fresh ET was 19.1%, and after frozen ET was 13.1%. The perinatal mortality rate per 1,000 births after non-donor fresh ET was 16.3 and after frozen ET was 8.6.

In terms of potential adverse effect, ICSI-conceived offspring has a greater neonatal morbidity, obstetric complications and congenital malformations, compared with spontaneous conception [2027-2029]. Additionally, epigenetic disorders and impaired neurodevelopment have been observed in infants born using ICSI compared with naturally conceived children [2005]. Among singleton infants born at 37 weeks of gestation or later, those following IVF had a risk of low birth weight that was 2.6 times (95% CI: 2.4–2.7) greater than in the general population (absolute risk of low birth weight with spontaneous vs. resulting from IVF was 2.5% vs. 6.5%) [1636]. Singleton infants after IVF were 39% more likely (adjusted RR: 1.39, 95% CI: 1.21–1.59) to have a non-chromosomal birth defect (particularly gastrointestinal and musculoskeletal) compared with all other singleton births. No single ART procedure (e.g., ICSI, fresh, or frozen ETs) was found to substantially increase the risk of birth defects.

Analyses from the Massachusetts Outcome Study of ART reported a 50% increase (adjusted prevalence ratio of 1.5, 95% CI: 1.3–1.6) in birth defects in infants after IVF vs. spontaneous pregnancy, and a 30% increase (adjusted prevalence ratio of 1.3, 95% CI: 1.1–1.5) in birth defects in infants after subfertility vs. spontaneous pregnancy [2030-2032]. No difference in risk of cancer was found between ART-conceived children and those spontaneously conceived [2033].

Health differences between ICSI and IVF conceptions have not been comprehensively assessed and results are contradictory. Some authors found a significantly reduced risk of birth defects in IVF compared to ICSI conceived infants [1639], while two meta-analyses demonstrated no difference in risk of congenital malformations between IVF and ICSI conception [1642, 2034]. Data about ICSI- and IVF-conceived adolescents or young adults are scarce but it seems that there is no difference in outcomes between the two techniques. Further research into health outcomes in adolescence and adulthood is required before conclusions can be drawn about the long-term safety of ICSI compared to IVF [2035].

10.8 Psychosocial aspects in men's infertility

Male infertility impacts men's psychological well-being in different ways. It results in emotional distress and challenges men's sense of identity. Factors such as personality style, sociocultural background, and treatment specificities (e.g., repeated cycles, treatment side-effects), may determine men's adjustment to infertility [2036]. The effects may be particularly worst in socially isolated men, with an avoidant coping style [2037]. Infertility-associated distress and psychiatric morbidity in men are further related to the male and mixed factor and increases after the clinical diagnosis [2038]. Within this regard, special attention has been given to men's psychological adaptation after the failure of medically assisted reproduction treatments. While the risk factors for emotional maladjustment encompass difficulties in couples' communication or avoidance/religious coping style from the female partner, the protective factors include seeking information, reframe infertility by assigning it a positive meaning, having social and spouse support, and talk openly about the infertility issue [2039]. Is worth noting that a failed treatment often results in a prolonged grief response, requiring post-treatment psychological support [2040]. Indeed, the literature supports the relevance of addressing men's psychological needs, as a means to reduce the impact of infertility treatments across all of its stages. The mental health expert is thus regarded as part of the infertility intervention team, acting in all intervention stages, using strategies that may range from psycho-education techniques to more comprehensive psycho-therapeutic approaches [2041]. Furthermore, there should be a deeper focus on preventive policies; It has been recognised that men, such as women, want to become parents. Yet, they have very limited knowledge on infertility related risk factors, including a lack of awareness on the age-related decline in fertility, and tend to overestimate the chance of spontaneous conception [2042, 2043].

11. LATE EFFECTS, SURVIVORSHIP AND MEN'S HEALTH

The EAU Guidelines Panel of Sexual and Reproductive Health have extensively reviewed the literature to provide guidance on: (i) late effects of urological diseases (both occurring during childhood and adulthood) on male sexual and reproductive health; (ii) late and long-term effects of cancers on male sexual and reproductive health; and, (iii) future directions to support personalised medicine strategies for promotion and raising the awareness of male sexual and reproductive health overall.

A systematic literature search for original English-language publications and review articles published up to December 2019 and a further search up to December 2020 were performed using both Pubmed and Google, yielding only a limited number of papers addressing the role of health care professionals in supporting male patients who have suffered from cancers in terms of sexual and reproductive health, or the concept of Men's Health programmes.

Despite considerable public health initiatives over the past few decades, the Panel has observed that there is still a significant gender gap between male and female in life expectancy [2044]. The main contributors to male mortality in Europe are non-communicable diseases (namely CVDs, cancer, diabetes and respiratory disease) and injuries [1679], as highlighted in a recent WHO report disproving the prevailing misconception that the higher rate of premature mortality among men is a natural phenomenon [2044, 2045]. The recent pandemic situation linked with SARS-CoV-2 infection associated diseased (COVID-19) further demonstrates how the development of strategies dedicated to male health is of fundamental importance [61].

The WHO report also addresses male sexual and reproductive health which is considered under-reported, linking in particular male infertility, as a proxy for overall health, to serious diseases in men [1934, 1939, 1940, 2046-2048]. These data suggest that health care policies should redirect their focus to preventive strategies and in particular pay attention to follow-up of men with sexual and reproductive complaints [1942, 2049]. [2049]. Considering that infertile men seem to be at greater risk of death, simply because of their inability to become fathers, is unacceptable [1943]. The Panel aims to develop a concept of a more streamlined and holistic approach to men's health.

For these guidelines, the Panel aimed to challenge clinicians to look beyond the pathology of disorders alone and consider the potential associations with other health disorders. Men with varicoceles have a higher incidence of heart disease and higher risk of diabetes and hyperlipidaemia following diagnosis [2049]. A diagnosis of infertility may have a profound psychological impact on men (and their partners), potentially

resulting in anxiety, enduring sadness, anger, and a sense of personal inadequacy and "unmet masculinity" [2038]. A combination of factors, personality, sociocultural background, and specific treatments/professional support, will determine how men cope with this diagnosis [2041].

The most common cancer among European men (excluding non-melanoma skin cancer) is PCa [399]. Due to new therapeutic approaches, survival rates have improved significantly [2050] and as men live longer, health-related quality of life and related sexual well-being will become increasingly important [389]. Regardless of the type of treatment used [1692], sexual dysfunction and distress are common post-treatment complications [390, 2051-2053].

Furthermore, little is known about the relevance of fertility and fertility-preservation strategies in cancer survivors [1931, 2054-2057]. In PCa, it has been documented that the psychological consequences persist, even after complete remission or cure and erectile function is restored [2058]. In addition, special attention must be given to gay and bisexual men with PCa; these men present specific sexual concerns steaming from heteronormativity standards that have a negative impact in health care quality [2059]. Therefore urologists dealing with sexual and reproductive health are primed to act as a vanguard for cancer survivorship programmes.

Finally, the relationship between ED and heart disease has been firmly established for well over two decades [315, 316, 318, 2060-2063]. Cadiovascular disease is the leading cause of both male mortality and premature mortality [2064-2067]. Studies indicate that all major risk factors for CVD, including hypertension, smoking and elevated cholesterol are more prevalent in men than women [2068-2074]. Given that ED is an established early sign of atherosclerotic disease and predicts cardiovascular events as an independent factor [318], it provides urologists with the unique opportunity for CVD screening and health modification and optimise CVD risk factors, while treating men's primary complaint (e.g., ED). Currently, both the EAU and AUA guidelines recommend screening for CVD risk factors in men with ED and late onset hypogonadism [2075-2077] (see Sections 3.7.3 and 5.2).

There is clearly a need to prospectively collect data addressing all aspects of male health, including CVD screening protocols and assess the impact of primary and secondary preventive strategies. The EAU Sexual and Reproductive Health Guidelines Panel aims to promote and develop a long-term strategy to raise men's health at a global level.

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13. CONFLICT OF INTEREST

All members of the EAU Sexual and Reproductive Health Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publicly accessible through the European Association of Urology website http://www.uroweb.org/guidelines/. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

14. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
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EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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Appendix 1

Table on medical management of ischaemic priapism

Author	Intervention Types (N, %)	Resolution of Priapism	Requirement for surgical management of refractory priapism	Sexual dysfunction	Side effects/ complications	Comments
Ateyah	122= Conservative Methods (122, 100%) Corporeal aspiration (92, 75,4%), Corporeal irrigation (70, 57.4%), Intracavernosal Sympathomimetics (10, 8.2%)	Conservative Methods (30, 24.6%), Corporeal aspiration (22, 23.9%), Corporeal irrigation (55, 78.57%), Intracavernosal Sympathomimetics (10, 100%)	NR	NR	NR	
Baker	9= Corporeal Aspiration (7,77.7%), Antiandrogens (9, 100%)	Immediate 5 (55.5%), total 8 (88.8%)	1 (11.1%)	NR	3 (33.3%)	
Bansal	9= Corporeal irrigation (9, 100%)	6 (66.6%)	NR	NR	NR	
Bardin	10= Corporeal Aspiration (10, 100%), Corporeal Irrigation (10, 100%), Intracavernosal Sympathomimetics (4, 40%)	7 (70%)	3 (30%)	NR	4 (40%)	
Deholl	9= Corporeal Aspiration (9, 100%), Corporeal Irrigation (9, 100%), Intracavernosal Sympathomimetics (6, 66.6%)	6 (66.6%)	3 (33.3%)	NR	NR	
Dittrich	36 Intracavernosal sympathomimetics (100%)	36 (100%)	1 (2.7%)	NR	NR	
El-Bahnasawy	50 Corporeal Aspiration (100%), Intracavernosal Sympathomimetics (100%)	Immediate 9 (18%), total 29 (58%)	NR	NR	NR	
Farrer 1961	14 Conservative Methods (11, 78.4%), Corporeal Aspiration (14, 100%), Corporeal Irrigation (14, 100%)	1 (7.1%)	NR	8 (57.1%)	Corporeal fibrosis 1 (7.1%), time point NR	
Forsberg 1981	9- Corporeal Aspiration (9,100%), oestrogens, sedatives, anticoagulants and anticholinergics (9, 100%) - epidural block (1, 11.1%)	NR	NR	6 (66.6%)	NR	
Gordon 2005	6= Conservative Methods (4, 66.7%), Intracavernosal sympathomimetics (2, 33.3%)	6 (100%)	0	1 (16.7%)	NR	

Govier 1994	24= Terbutaline 5mg, (8, 33.3%), Terbutaline 2.5mg, (7, 29.2%), Placebo (9, 37.5%)	13 (54.2%)	Terbutaline 6mg 3 (37.5%) vs Placebo: 5 (55.6%), Terb 2.5mg 3 (42.9%), p>0.05	NR	NR	
Grace 1968	17- Conservative Methods (17, 100%), Corporeal Aspiration (5, 29.4%), Pharmacological intervenions: anticoagulants 3, stilebstrol 3 (6, 35.3%)	non-systematic reporting - immediate resolution is <5%	NR	NR	wound infection,	
Habous 2016	53= Conservative Methods (53, 100%), Corporeal Irrigation (14, 26.4%), Intracavernosal Sympathomimetics (3, 5.7%), Pharmacological Interventions: salbutamol (32, 60.4%)	Exercise: 21 (39.6%), salbutamol 18 (34%), aspiration + irrigation saline 11 (20.75%), 3 phenylephrine (5.7%)	0%	NR	0%	
Hubler 2003	5= Intracavernosal sympathomimetics (Methylene Blue, 5, 100%)	Immediate 3 (60%), total 5 (100%) in 24 hours	0%	all had ED pre-intervention	haematoma 5, burning sensation 5 (100%)	
Jiang 2014	44= Intracavernosal sympathomimetics: Phenylephrine (44, 100%)	44 (100%	0%	Unclear but 18/44 had ED pre-procedure	throbbing sensation but unclear whether this was from phenylephrine or alprostadil	
Kadioglu 1995	9= Intracavernosal sympathomimetics (Methylene Blue, 9, 100%)	9 (100%)	0%	3 (33.3%) reported ED at 3 weeks; at 6 weeks, 1/3 had ED	pain 9 (100%)	
Keskin 2000	19= Intracavernosal Sympathomimetics (adrenaline, 19, 100%)	Immediate 10 (53%), total 18 (94.7%)	0%	0%	0%	
Khurana 2002	9- conservative Methods (cold enema, 9, 100%), Corporeal Irrigation (1/9, 11.1%)	enema 5 (55.5%) , aspiration 1 (11.1%)	NR (3 pts referred to urological center for further management)	NR	NR	
Kulmala 1996	53= Conservative Methods (16, 30.2%), Corporeal Aspiration (8, 15.1%), Corporeal Irrigation (17, 32.1%), Intracavernosal Sympathomimetics (12, 22.6%)	NR	NR	Conservative 5 (31%), Incision + Aspiration 3 (38%), Puncture + Lavation 12 (71%), Puncture +Alpha sympatho-mimetics 11 (92%)	NR	

Kumar 2019	71 (no separate results on 69non-SCD pt): Corporeal Aspiration (71, 100%), some of the pts had phenylephrine but number unclear	15 (21%) no separate results on non-SCD pts	NR	NR	NR	
Larocque 1974	23= Conservative Methods (16, 69.6%), Corporeal Aspiration (7, 31.3%)	Conservative (5, 31.2%, includes various ways of management such as sedation, analgesics, exercise, ice packs, stilbestrol, enema, oxygen, proteolytic enzymes, epidural anaesthesia, sodium bicarbonate, low molecular weight dextran), aspiration (2, 28.6%)	NR	NR	NR	
Lowe 1993	75= Pharmacological Interventions: (25 oral terbutaline, 25 oral pseudoephedrine, 50 placebo)	Terbutaline 9 (36%), Pseudoephedrine 7 (28%), Pbo 3 (12%), Terbutaline sig >Pbo	0%	NR	NR	All non-responders were offered aspiration and irrigation (successful in all)
Martinez Portillo 2001	12= Corporeal Aspiration (12, 100%), Corporeal Irrigation (12, 100%), Intracavernosal Sympathomimetics (2, 17%), Pharmacological Intervention (1, 8%)	Total 10 (83.3%%), all with corporeal injection	NR	no change in baseline ED function in patients with priapism due to corporeal injections. Leukaemia patient regained potency. Idiopathic patient impotent.	Temporary side effects: Burning sensation in 6/12, blue dis-colourisation in 4/12	
Molina 1989	12= Corporeal Aspiration (12, 100%), Corporeal Irrigation (12, 100%), Intracavernosal Sympathomimetics (12, 100%)	Irrigation and epinephrine, 10 (83.3%)	NR	Not specified individual data, "all patients who were spontaneously potent before continued to be potent"? 11/16	NR	
Moloney 1975	5= Conservative management, Corporeal Irrigation, Pharmacological Intervention (5, 100%, exact numbers not specified)	Unclear, but likely 5, 100%	NR	2(40%)	NR	

Muruve 1996	9= Intracavernosal Sympathomimetics (9, 100%)	Total 9, 100%; Sympathomimetics 8 (88.9%). Symapthomimetics followed by corporeal aspiration: 1 (11.1%)	0(0%)	NR	minor haematoma in 1 patient	
Pal 2016	19= Corporeal Aspiration (2, 11%), Intracavernosal Sympathomimetics (17, 89%)	Aspirin and ICI: 3 (15.8%)	16(84%)	Unclear; 2/3 patients treated with aspiration and ICI had preserved erectile function	NR	
Pantaleo-Gandais 1984	35= Conservative Methods (35, 100%)	Conservative management 4 (11.4%)	31(88.57%)	Good sexual function in only 1/4 responders	NR	Mixed SCD and non-SCD population
Passavanti 2009	17= Corporeal Aspiration (17, 100%), Corporeal Irrigation (17, 100%), Intracavernosal Sympathomimetics (7, 41%; adrenaline 5, and adrenaline + ethylephrine 2), Intracorporeal Sympathomimetics (Methylene Blue)	Total 12, (70.6%, 10 purely from methylene blue and aspiration and irrigation; 2 required additional ICI adrenalaine)	4(24%)	NR	NR	
Priyadarshi 2004	68= Pharmacological Interventions (34 Terbutaline, 34 Placebo, 100%)	42% terbutaline group vs 15% placebo gp ($p<0.05$).	NR	NR	Tacycardia 34(30%)	
Ridyard 2016	50 (mixed SCD and non-SCD pts): Intracavernosal Sympathomimetics: (38, 65%; phenylephrine alone), Intracavernosal Sympathomimetics and Corporeal Irrigation: (12, 21%; phenylephrine and irrigation)	42 (84%)	overall 8(14%) [ICI (0%), idiopathic (14%), scd (0%), psychiatric medicines (37%), cocaine(05), PDE5inhibitors (0%), other (100%))	NR	0(0%)	
Zhao	136 episodes= Conservative Methods (25, 14.8%), Corporeal Aspiration/Irrigation (4, 2.4%), Intracavernosal Sympathomimetics (19, 11.4%), Combination of Corporeal Aspiration/ Irrigation and Sympathomimetics (119, 70.4%)	141 (84.6%)	26 (15.4%)	NR	NR	
Watters	17= Intracavernosal Sympathomimetics (17, 100%)	16 (94%)	1(6%)	NR	NR	

Vorobets	10= Intracavernosal Sympathomimetics (10, 100%)	0 (0%)	10 (100%)	NR	NR	
Van Driel	8= Corporeal Aspiration (8, 100%), Intracavernosal Sympathomimetics (8, 100%)	6 (75%)	2(25%)	NR	NR	
Ugwumba	7= Corporeal Aspiration (7, 100%), Corporeal Irrigation (7, 100%), Intracavernosal Sympathomimetics (1, 14%)	0	7(100%)	NR	NR	
Torok	72= Corporeal Aspiration (72, 100%), Intracavernosal Sympathomimetics (72, 100%)	72 (100%)	0(0%)	NR	NR	
Stief	29= Corporeal Aspiration (3, 10.3%), Intracavernosal Sympathomimetics (26, 89.7%)	29 (100%)	NR	NR	NR	
Sonmez	46= Corporeal Aspiration (46, 100%), Corporeal Irrigation (46, 100%), Intracavernosal Sympathomimetics (4, 8.7%)	39 (84.7%)	7(15.3%)	NR	NR	
Soler	14= Conservative Methods (14, 100%), Corporeal Aspiration (2, 14%), Pharmacological Interventions (14, 100%)	14 (100%)	0(0%)	NR	piloerection	
Serrate	23= Intracavernosal Sympathomimetics (23, 100%)	23 (100%)	NR	NR	NR	
Saffoncuartas	31= Conservative Methods (31, 100%), Corporeal Aspiration (1, 3.2%), Corporeal Irrigation (1, 3.2%), Intracavernosal Sympathomimetics (19, 61.3%), Pharmacological Interventions (1, 3.2%)	31 (100%)	NR	NR	NR	

Appendix 2

Table on Surgical shunts in ischaemic priapism

Study	n	Non-Surgical Intervention (%)	Surgical Intervention (n/ %)	Resolution of priapism (%)	Sexual function	Surgical adverse event
Kumar *et al*. 2019	71	Penile aspiration +/- alpha adrenergic agonist irrigation n=24 (33%)	Distal shunt n=38(53%) [Winter shunt (n=30), Ebbehoj (n=6), Al-Ghorab (n=2)] Proximal shunt n=9(12%) [Quackle(n=6,) Grayhack (n=3)]	Distal shunt 42.01% Proximal shunt 55.55% Penile aspiration 21.12%	21 (29.57%) patients followed up at 6 months n=15 (71.4%) reported moderate to severe ED	Complication following shunts (n=20, 42.5%) [Wound infection n=5, Shunt site bleeding n=14, skin necrosis n=1]
Lian *et al*. 2010	12	-	Corporospongiosal shunt with intracorporeal tunnelling (n=12)	100%	Average FU 21.6+/-10.1 months IIEF5 score 11.7+/-6.3 post treatment (vs 23.7+/- 1.1 prior to priapism)	No severe complications noted
Macaluso *et al*. 1985	34	n=29 (85.2%) had initial conservative treatment	12/29 patients (41.3%) required surgery with Winter's shunt	100% with Winter's shunt	-	Overall complications from surgery 5/12 (41.6%) [Urethral injury (n=1), Penoscrotal haematoma (n=3), Epididymitis (n=1)]
Moloney *et al*. 1975	11	-	Saphenocavernous bypass (n=12)	100%	70% 'good' if functional outcome' and 30% 'fair functional outcome'	-
Muneer *et al*. 2008	60 (stuttering)	100% initial non-surgical treatment	Surgical procedures in n=12 [Penile prosthesis n=3, embolisation n=5, Winter shunt n=1. El-Ebbehoj n=1, Cavernosal ligation n=1)	Success rate 100% for Penile prosthesis, 20% for embolisation and 0% for other surgical therapies	-	-
Nelson *et al*. 1976	48	-	Winter's shunt (n=8) Saphenocavernous bypass (n=3)	Shunt success 10/11 (failed in single case when done in priapism due to sickle cell disease)	50% potency rate in patients treated by aspiration followed by shunting	-
Nixon *et al*. 2003	28	-	Winter's shunt (n=14) Al Ghorab Shunt(n=13) Quackle shunt (n=1)	Winters shunt 14.2% (n=12 required reoperation) Al Ghorab 92% (n=1 required reoperation) Quackle 100% success	2/20 available patients for FU (10%) had preserved erectile function following shunt surgery	-

Pantaleo-Gandais *et al*. 1984	35	100% had initial conservative management	Surgery required in 31 cases (88.57%) [corporocavernosal incision n=8, cavernous spongiosum shunt n=9, cavernous-saphenous shunts n=4, Ebbehoj n=9, Winters n=1)	Overall 85.7% success across all shunts	100% preservation of sexual function if priapism <3 days duration (n=17) 11.1% preservation of sexual function if priapism>3days	-
Ugwumba *et al*. 2015	15	13/15 (86.6%) had initial conservative treatment prior to shunting	Glanulo-cavernous (Al-Ghorab) shunt n=15 (100%)	Immediate detumescence (n=14,93.3%) Delayed detumesence (n=1, 6.7%)	46.7% ED ED increased if presentation was >24h	
Lawani *et al*. 1999	66	100% had initial conservative treatment	Surgical procedures in 53/66 (80.3%) [bilateral cavernotomies n=23, cavernoglandular shunt n=11, cavernospongiosal shunt n=18, cavernosaphenous shunt n=1]	100% immediate detumesence post-surgery	50% ED rate in 12 patients who had follow-up	-
Pal *et al*. 2016	19	100% had aspiration prior to surgery	16/19 (84%) had surgery [Winter's shunt (n=16) Al Ghorab shunt (n=6) Quackle shunt (n=5)]	18.7% Winter's shunt 66.7% Al Ghorab shunt 62.5% Corporal snake 60% Quackle's shunt	Preservation of erectile function 66.7% for aspiration only 18.1% for proximal shunts 20% for distal shunts	N=3 (15.7%) had complications [urethral injury n=1, cavernositis n=1, skin necrosis n=1)
Wendel *et al*. 1981	8	-	Corporo cavernosa – glans penis shunt (n=8)	87.5% success rate	-	-
Kihl *et al*. 1980	31	-	Saphenocavernous shunting (n=26)	76.9% initial success 23.1% required further shunting	7/26 (26.9%) potent at months – 10 yrs	N=5 (19.2%) complication rate [Urethrocutaneous fistula n=1, haematoma n=2, thrombophlebitis n=1, altered sensation n=1]
Kilinc *et al*. 2009	15		Cavernosal-cephalic vein shunt (n=15)	86.6% success (n=2 required further saphenocaver-nosal shunt)	3/13 (23) reported ED at 12 months	No major complications reported
Klufio *et al*. 1991	20		Al Ghorab shunt (n=20)	All had immediate detumescence (100%)	39% potency rate	10% complication rate (post-operative bleeding n=2)
Adeyato *et al*. 2009	54	N=19 (35%)	N= 35 (65%) Ebbhoj's shunt	2/35 (5.7%) had recurrence in the immediate postop period	Potency rate 47.37% conservative vs 70.37% for shunt	-

Aghagi *et al*. 2000	35	All had prior conservative treatment	N=35 had surgery [Perineal cavernospongiosal shunt (n=14), modified corporospongiosal shunt (n=21)]	100% detumesence postop	8/35 (22.8%) had absent erections post-surgery	-
Brant *et al*. 2009	13	All had prior conservative treatment	T shunt (n=13)	12/13 (92%) had resolution (n=1 required further T shunt)	84.6% erectile function	No major surgical complications
Canguven *et al*. 2013	15	-	Transient distal penile shunt	10/15 (66% success rate)	-	-
Carter *et al*. 1976	12	-	Corporosaphenous shunt (n=2) Cavernospongiosum shunt (n=10)	Not clear	100%ED in corporosaphenous shunt 4/7 (57.1%) potency rate following cavernospongio-sus shunt	
Chary *et al*. 1981	8	-	Caverno-glandular shunt (n=8)	100% success	50% potency rate	(n=1 cavernositis, 12.5%)
Klein *et al*. 1972	9	-	Corpus saphenous shunt (n=9)	22.2% (n=2) had partial response immediately	11.1% potency rate	

Appendix 3

Table on penile prosthesis insertion for ischaemic priapism

Study	n	Non-Surgical Intervention (%)	Surgical Intervention (n/ %)	Resolution of priapism (%)	Sexual function	Surgical adverse event
Rees *et al*. 2002	8	All had prior conservative treatment	Penile prosthesis n=8 (4 had prior shunt)	All implants successful (mean duration of priapism at presentation 91h)	7/8 (87.5%) sexually active 100% satisfaction in those sexually active	N=1 penile deformity for revision due to fibrosis around cylinder
Zacharakis *et al*. 2014	95	All had prior conservative treatment	N=68 penile implants (early median 7 days) vs n=27 delayed implants (median of 5 months)	100%	25/95 (26.3%) able to have intercourse Satisfaction 96% for immediate implant vs. 60% for delayed group	13/95 (13.6%) required revision surgery due to complications
Salem *et al*. 2010	12	All had prior conservative treatment	12 acute	100%	100% achieved intercourse	No revision surgery required No postoperative complications noted
Sedigh *et al*. 2011	20	N=6 non-surgical treatment	N=10 shunts (n=5 of those had early penile prosthesis)	100%	100% satisfaction with prosthesis 100% of penile prosthesis group sexually active	No complications from prosthesis insertion
Zacharakis *et al*. 2015	10	-	N=10, malleable penile prosthesis	100%	80% satisfaction as per IIEF at 3 months	No erosion or urethral injury noted

Appendix 4

Table on series of early and delayed penile prosthesis implantation secondary to priapism

Study	n: early/ delayed	n: priapism/ total	n: malleable/ inflatable	Technique	Mean follow-up (months)	Complications	Outcomes
Small [2078]	0/4	4/4	3/0	Sharp dissection	38	inability (1)	Success (3)
Bertram *et al.* [2079]	0/6	6/6	4/1	Sharp dissection	N/A	inability (1)	Success (5)
Kelami [2080]	0/12	12/12	12/0	N/A	N/A	N/A	N/A
Mireku-Boateng [2081]	2/0	2/2	2/0	N/A	36	-	Success (2)
Douglas *et al.* [2082]	0/5	5/5	5/0	Excavation	48	Urethral erosion (2), revision (1)	Success (4)
Kabalin [2083]	0/1	1/1	1/0	corporotomy	N/A	Inability to insert inflatable prosthesis	Success (1)
Knoll *et al.* [2084]	0/20	2/20	0/20	Downsized device	20	Infection (1), mechanical failure (1), hypoesthesia (2)	Success (19)
Herschorn *et al.* [2085]	0/11	2/11	2/9	PTFE graft	46	Revision (3)	Success (8)
George *et al.* [2086]	0/12	2/12	7/5	Scar excision (12), PTFE graft (1)	22	Perforation (1), malfunction (1)	Success (11)
Sundaram [2087]	1/0	1/1	0/1	N/A	8	-	Success (1)
Upadhyay *et al.* [1402]	1/0	1/1	1/0	N/A	6	-	Success (1)
Rajpurkar *et al.* [2088]	0/34	4/34	11/23	Multiple incisions+ scar excision	23.7	Perforation (1), malfunction (1)	Success (34)
Mooreville *et al.* [2089]	0/16	3/16	0/16	Cavernotom+ Downsized (14)	N/A	Perforation (6), crossover (3)	Success (16)
Ghanem *et al.* [2090]	0/17	5/17	10/7	Corporal counter incision	N/A	Perforation (1)	Success (17)
Park *et al.* [2091]	0/1	1/1	0/1	Narrow base, evaporisation	12	-	Success (1)
Montague *et al.* [2092]	0/9	4/9	0/9	Excavation, downsized (7)	44	Malfunction (1)	Success (9)
Shaeer [2093]	0/12	4/12	8/4	Shaeer excavation	N/A	-	Success (12)
Durazi *et al.* [2094]	0/17	17/17	11/6	Corporotomy + partial excavation	22.7	Urethral injury (2)	Success (17)
Lopes *et al.* [2095]	0/8	3/8	8/0	Bovine pericardium graft	32	-	Success (5)
Ralph *et al.* [1399]	50/0	50/50	50/0	Hegar dilator	16	Infection (3), revision for erosion (3), cylinders too short (2), autoinflation (1), penile curvature (1)	Success (48)
Salem *et al.* [1400]	12/0	12/12	12/0	N/A	15	Significant penile shortening	Success (12)
Stember *et al.* [2096]	0/1	1/1	0/1	Narrow base, sharp corporal excision	3	Urethral injury (1)	
Sedigh *et al.* [1401]	5/0	5/5	1 /4	N/A	N/A	Urethral injury (1)	Success (5)

Bella *et al.* [1404]	0/5	5/5	0/5	Rosello dilator	N/A	Urethral injury (1)	Success (5)
Egydio *et al.* [2097]	0/69	24/69	57/12	Double-windsocks	22.5	Urethral injury (4)	Success (42), Somewhat satisfaction (19)
Razzaghi *et al.* [2098]	14/0	14/14	14/0	N/A	14	-	Success (14)
Zacharakis *et al.* [1311]	68/27	95/95	76/19	Downsized (15 in delayed group)	17	Infection (5), penile curvature (1)	96% success in early group / 60% success in delayed group
Tausch *et al.* [2099]	14/0	14/14	14/0	N/A	N/A	Infection (1), distal extrusion (1) Urethral injury (1)	Success (14)
Faddan *et al.* [2100]	1/0	1/1	1/0	N/A	N/A		Success (1)
Bozkurt *et al.* [2101]	0/2	1/2	1/1	Use of microdebrider for excavation	12	-	Success (2)
Tsambarlis *et al.* [1405]	0/13	2/13	0/13	use vacuum device preoperatively	N/A	Infection (1), revision (1)	Success (12)
Hebert *et al.* [2102]	30/42	14/72	0/72	Rosello dilator, downsized (63)	12	urethral injury (2), corporal perforation (15), cross-over (5), inability to dilate (1), infection (3), urethral erosion (2), glans erosion (7)	87% success in early group / 67% success in delayed group
Summary	198/344	317/542	311/229	Excavation, Shaeer technique, Rosello cavernotome, excision of scar, downsized prothesis with grafting	22.4	Infection: early 1-10% / delayed 3-20% Perforation, crossover or erosion: early 11% / delayed 13% Urethral injury: early 1% / delayed 3%	Success rate: early 87-100% / delayed 60-100%

Appendix 5

Table on embolisation for non-ischaemic priapism

Study	n	Non-Surgical Intervention (%)	Surgical Intervention (n/ %)	Resolution of priapism (%)	Sexual function	Surgical adverse event
Bastuba *et al*. 1994	7	-	Embolisation (n=7) post traumatic	100% resolution between 4 – 126 days	Full erectile function return at 2weeks-5months	-
Bartsch *et al*. 2004	9	-	Embolisation (n=9) post trauma	8/9 (88.8%) success; once case required repeat embolisation	100% potency at 4 weeks	Coil displacement in1 case requiring repeat procedure
Baba *et al*. 2007	6	-	Embolisation (n=9) with gelatine sponge or microcoil	Detumesence achieved in 83.3% at 1 months and 100% within 'few months'	100% normal erectile function at 5 years	-
Liu *et al*. 2008	8	-	Embolisation with gelatine (n=2, 25%) Embolisation with microcoil(n=6, 75%)	100% redo embolisation in gelatine group at 1 week 100% success rate from microcoil embolisation	Mean IIEF 22.2 at 6 months post embolisation	-
Miller *et al*. 1995	5	-	Embolisation with gelatine (n=4) Embolisation with autologous clot (n=1)	100%	-	-
Numan *et al*. 2008	11	-	Embolisation with autologous clot (n=11)	100% initial success Repeat embolisation required in 27.2% (n=3)	100% erectile function restoration at 6 weeks	-
Kim *et al*. 2007	27	-	Embolisation (autologous clot n=12, gelatine sponge n=12, microcoil and Sponge n=1, polyvinyl n=1, Nbutylcyanoacrylate n=1)	89% following first embolisation 7% required repeat embolization 4% subsequent shunt surgery	No change in premorbid erectile function (78%)	
Cantasdemir *et al*. 2010	7	-	Embolisation (n=7)	6/7 (85.7%) complete detumescence (n=1 required redo embolisation)	No signs of ED detected at mean FU of 6 years	-
Chick *et al*. 2018	20	-	Embolisation using autologous clot, micocoil, polyvinyl or combination (n=20)	18/20 (90%) success	Mean IIEF score post embolisation 25.8	-
Ciampalini *et al*. 2002	10	-	Embolisation (n=9, 90%) Artery ligation (n=1, 10%)	44% recurrence rate following first embolisation	Sexual function preserved in 80%	-
DeMagistris *et al*. 2020	9	-	Embolisation with microcoils, microparticles or spingostran (n=11)	100% immediate detumescence 2/9 (22% required retreatment at 1-2 weeks)	Erectile function preserved compared to premorbid state	No major complications
Gorich *et al*. 2002	6	-	Embolisation with gelatine (n=3) and microcoil (n=3)	100% success	100% potency	-

EAU Guidelines on

Testicular Cancer

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1. INTRODUCTION

1.1 Aim and objectives

The aim of these guidelines is to present the current evidence for the diagnosis and treatment of patients with cancer of the testis. Testicular cancer (TC) represents 5% of urological tumours affecting mostly younger males. This document addresses post-pubertal testicular germ-cell tumours (TGCTs) in the male including spermatocytic tumour and sex cord/gonadal stromal tumours.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions which should also take personal values and references/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on TC consists of a multidisciplinary group of clinicians including, urologists, medical oncologists, a radiation-oncologist, and a pathologist. When necessary, consultants from other specialties provide input. Members of this Panel have been selected, based on their expertise, to represent the professionals treating patients with TC. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/testicular-cancer/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available, as are a number of translations of all versions of the EAU Testicular Cancer Guidelines. All documents are accessible through the EAU website: http://www.uroweb.org/guideline/testicularcancer/.

1.4 Publication history and summary of changes

1.4.1 Publication history

The EAU published the first guidelines on TC in 2001. Since 2008, the TC Guidelines contains a separate chapter on testicular stromal tumours. This document presents a limited update of the 2021 publication. Review papers have been published in the society's scientific journal European Urology, the latest version dating to 2015 [1].

1.4.2 Summary of changes

For the 2022 Testicular Cancer Guidelines, new references have been added throughout the document. Key changes in this publication include:

- The chapter on stromal tumours has been re-structured and revised under a new heading: "Rare adult para- and testicular tumours";
- All the chapters have been reviewed and supporting text and recommendations across the guideline have been rephrased and revised;
- Summaries of evidence have been added throughout the text;
- Old citations have been refreshed and replaced with newer references;
- A number of articles identified after the scope search cut-off date have been included as they contain important information pertaining to guidelines recommendations;
- The recent re-validation of the 1997 International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic risk-factor based system for metastatic testicular Germ cell tumours in patients treated with cisplatin-etoposide as first-line chemotherapy has been included in the text replacing the old version with the corresponding references;
- New supporting text regarding VTE prophylaxis in males with metastatic germ cell tumours (GCTs) receiving chemotherapy has been added.

2. METHODS

New and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence only (i.e., systematic reviews with meta-analysis, randomised controlled trials [RCTs], and prospective non-randomised comparative studies)

published in the English language. The search was restricted to articles published between April 2020 and June 2021 and included testicular stromal tumours. Databases covered by the search included PubMed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 1,959 unique records were identified, retrieved and screened for relevance. Fifty-eight new and updated references have been included in the 2022 Guidelines. A detailed search strategy is available online: http://uroweb.org/guideline/testicular-cancer/?type=appendices-publications.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [2, 3]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: www.uroweb.org/guidelines.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.1 Review

The 2020 Guidelines document was subjected to peer-review following publication.

2.2 Future goals

- A systematic review on diagnostic accuracy on value of the ultrasound (US) in the diagnostic of small testicular masses in collaboration with the Sexual and Reproductive Health has been produced and is under peer-review.
- A review and discussion of the recommendations with patient associations is ongoing.
- The development of a TC survivorship plan in collaboration with patient associations is planned.
- An Individual Patient Data (IPD) prognostic factor study on the value of pathological factors in clinical stage I seminoma testis patients under active surveillance approved by the Guidelines Office Methods Committee and including data from with five international centres is presently in the analysis phase.
- Care Pathways on diagnostic, treatment CS I, and treatment of metastatic disease and Cheat Sheets on TC are being prepared in collaboration with the EAU GO.

3. EPIDEMIOLOGY, AETIOLOGY & PATHOLOGY

3.1 Epidemiology and Aetiology

Testicular cancer represents 1% of adult neoplasms and 5% of urological tumours, with three to ten new cases per 100,000 males/per year in Western societies [6]. Its incidence has increased during recent decades, particularly in industrialised countries [7, 8], and continues to rise. At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumours (GCT) (90-95% of cases) [6]. The peak incidence is in the third decade of life for non-seminoma testis (NST) and mixed GCT patients, and in the fourth decade for seminoma testis (ST) patients. In 5% of TGCT patients the primary site is at an extragonadal location [9].

There are two fundamental categories of TGCTs based on their development and epigenetic features. Most malignant post-pubertal TGCTs (or type II GCT) originate from the germ cell neoplasia "*in situ*" (GCNIS). They

are clinically and histologically subdivided into seminomas and non-seminomas, the later encompassing somatic and extra-embryonal elements of embryonal carcinoma, yolk sac, choriocarcinoma and teratoma [10].

Non-related GCNIS tumours include pre-pubertal type teratoma and yolk sac (Type I), diagnosed at early paediatric age, and spermatocytic tumours (Type III), diagnosed in the elderly. Although there is overlapping histology between the pre-pubertal teratoma/yolk sac and the teratoma and yolk sac elements in the GCNIS-related non-seminomas, they have a separate and independent pathogenesis [10].

Overall, type II TGCT have a low mutational burden and few somatic changes. A specific recurrent genetic marker – an isochromosome of the short arm of chromosome 12 – (i12p) – is over-represented in most invasive GCNIS-related TGCTs [10, 11] but not found in GCNIS [12]. However, some type II TGCTs, mostly seminomas, appear to lack a gain of 12p and present preferential cKIT mutations. Without occurrence of these mutations GCNIS will not progress to invasive GCTs [10]. Other significant chromosomal aberrations in type II TGCTs are gain of 7, 8, 21 and loss of chromosomes 1p, 11, 13 and 18 [13].

Epidemiological risk factors for the development of TC are components of the testicular dysgenesis syndrome (which encompasses cryptorchidism), hypospadias, decreased spermatogenesis and impaired fertility [14-16] or disorders/differences of sex development [17]. Additional risk factors include family history of TC among first-degree relatives and the presence of a contralateral testicular tumour or GCNIS [14, 18-24]. Recent genome-wide association studies revealed detectable susceptibility loci leading to an increased relative risk to develop TC [25].

3.2 Histological classification

General:
The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification [26].

1. **Germ cell tumours**
   - Germ cell neoplasia *in situ* (GCNIS)
2. **Derived from GCNIS**
   - Seminoma
   - Embryonal carcinoma
   - Yolk sac tumour, post-pubertal type
   - Trophoblastic tumours
   - Teratoma, post-pubertal type
   - Teratoma with somatic malignant components
   - Mixed germ cell tumours
3. **Germ cell tumours unrelated to GCNIS**
   - Spermatocytic tumour
   - Yolk sac tumour, pre-pubertal type
   - Mixed germ cell tumour, pre-pubertal type
4. **Sex cord/stromal tumours**
   - Leydig cell tumour
     - Malignant Leydig cell tumour
   - Sertoli cell tumour
     - Malignant Sertoli cell tumour
     - Large cell calcifying Sertoli cell tumour
     - Intratubular large cell hyalinising Sertoli cell neoplasia
   - Granulosa cell tumour
     - Adult type
     - Juvenile type
   - Thecoma/fibroma group of tumours
   - Other sex cord/gonadal stromal tumours
     - Mixed
     - Unclassified
   - Tumours containing both germ cell and sex cord/gonadal stromal
     - Gonadoblastoma

5. **Miscellaneous non-specific stromal tumours**
   - Ovarian epithelial tumours
   - Tumours of the collecting ducts and rete testis
     - Adenoma
     - Carcinoma
   - Tumours of paratesticular structures
     - Adenomatoid tumour
     - Mesothelioma (epithelioid, biphasic)
     - Epididymal tumours
   - Cystadenoma of the epididymis
   - Papillary cystadenoma
   - Adenocarcinoma of the epididymis
   - Mesenchymal tumours of the spermatic cord and testicular adnexae

4. STAGING & CLASSIFICATION SYSTEMS

4.1 Staging

The 2016 Tumour, Node, Metastasis (TNM) classification of the International Union Against Cancer (UICC) is recommended to assess the anatomical extent of the disease (Table 4.1) [27].

Table 4.1: TNM classification for testicular cancer (adapted from UICC, 2016, 8th edn.) [27]

pT - Primary Tumour[1]	
pTX	Primary tumour cannot be assessed (see note[1])
pT0	No evidence of primary tumour (e.g., histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)+
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis**
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion**
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N - Regional Lymph Nodes – Clinical	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
Pn - Regional Lymph Nodes – Pathological	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis **
	M1a Non-regional lymph node(s) or lung metastasis
	M1b Distant metastasis other than non-regional lymph nodes and lung

S - Serum Tumour Markers (Pre chemotherapy)			
SX	Serum marker studies not available or not performed		
S0	Serum marker study levels within normal limits		
	LDH (U/l)	**hCG (mIU/mL)**	**AFP (ng/mL)**
S1	< 1.5 x N and	< 5,000 and	< 1,000
S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
S3	> 10 x N or	> 50,000 or	> 10,000

N indicates the upper limit of normal.

LDH = lactate dehydrogenase; hCG = human chorionic gonadotrophin; AFP = alpha-fetoprotein.

[1] Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

[+] The current "Carcinoma in situ" nomenclature is replaced by GCNIS.

[*] AJCC eighth edition subdivides T1 Pure Seminoma by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension [28].

[**] AJCC eighth edition considers the hilar soft tissue invasion as pT2, while the discontinuous involvement of the spermatic cord is considered as pM1 [28].

4.2 The Union for International Cancer Control prognostic groups

According to the 2016 TNM classification, the following prognostic groups are defined:

Table 4.2: Prognostic groups for testicular cancer (UICC, 2016, 8th edn.) [28]

Stage grouping	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1-N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1a	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1-N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1-N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

Stage IA: Patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchidectomy serum tumour marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalisation.

Stage IB: Patients have a more locally invasive primary tumour, but no sign of metastatic disease.

Stage IS: Patients have persistently elevated (and usually increasing) serum tumour marker levels after orchidectomy, indicating subclinical metastatic disease (or possibly a second GCT in the remaining testis).

In population-based patient series from developed countries, 75-80% of seminoma patients, and about 55%-64% of non-seminomatous germ cell tumour (NSGCT) patients have stage I disease at diagnosis [29, 30]. True stage IS (persistently elevated or increasing serum tumour marker levels after orchidectomy) is found in about 5% of non-seminoma patients [29].

4.3 The International Germ Cell Cancer Collaborative classification for the prognostic-risk groups of metastatic testicular cancer

The 1997 IGCCCG defined a prognostic risk-factor system for metastatic GCT based on identification of clinically independent adverse factors. The classification has been revalidated on a contemporary cohort of metastatic testicular GCT treated with cisplatin/etoposide based first-line chemotherapy.

Compared to the 1997 figures, the five-year progression-free survival (PFS) of non-seminoma patients was unchanged for good- and intermediate-risk, but significantly improved for poor-risk patients (from 41% to 54%). The five-year overall survival (OS) was substantially better for all groups. In addition to the traditional components of the IGCCCG risk-prognostic groups previously described, older age (linear association) and lung metastasis were confirmed as negative factors for PFS [31].

In seminoma, the five-year PFS increased to 89% and 79% in good- and intermediate-risk patients with the corresponding OS rates of 95% and 88%. Lactate dehydrogenase (LDH) proved to be an additional adverse prognostic factor. Good-prognosis patients with LDH above 2.5 times the upper limit of normal (ULN) had a three-year PFS of 80% and a three-year OS of 92%, vs. 92% and 97% (in the group with lower LDH) [32].

Table 4.3: Prognostic-based staging system for metastatic germ cell cancer (IGCCCG) [31, 32]*

Good-prognosis group	
Non-seminoma 5-year PFS 90% 5-year survival 96%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma 5-year PFS 89% 5-year survival 95%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma 5-year PFS 78% 5-year survival 89%	*Any of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma 5-year PFS 79% 5-year survival 88%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma 5-year PFS 54% 5-year survival 67%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as “poor-prognosis”

** Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day).*

AFP = alpha-fetoprotein; hCG = human chorionic gonadotrophin; LDH = lactate dehydrogenase; PFS = progression-free survival.

5. DIAGNOSTIC EVALUATION

5.1 Physical examination

Testicular cancer usually presents as a unilateral scrotal testicular mass detected by the patient, or as an incidental finding on US. Scrotal pain may be present in 27% of patients [33, 34] and a potential reason for delayed diagnosis in 10% of cases [33]. Around 1% of patients presenting with gynaecomastia have a germ cell or sex cord/gonadal tumour of the testes [35] and 11% present with back and flank pain [34]. As such, when there is suspicion of TC, physical examination must include abdominal, chest and supraclavicular exploration.

5.2 Imaging

*5.2.1 **Ultrasonography of the testes***

High-frequency (>10 MHz) testicular US should be used to confirm a testicular tumour even in the presence of a clinically evident testicular lesion [34, 36].

The use of testicular US can:

1. determine whether a mass is intra- or extra-testicular;
2. determine the volume and anatomical location of the testicular lesion;
3. be used to characterise the contralateral testicle – to exclude other lesions and identify risk factors for GCNIS (see section 5.4.4).

Testicular US is also recommended for all men with retroperitoneal or visceral masses and/or without elevated serum human chorionic gonadotropin (hCG) or alpha-fetoprotein (AFP) in the absence of a palpable testicular mass; and for fertility work-up evaluation [34, 36-38].

A range of modalities of US have been investigated (B-mode, dynamic contrast enhanced, real-time elastography, and shear wave elastography) in small cohorts to determine if these can distinguish between benign and malignant testicular lesions [39-42]. So far, the results are not reliable enough to replace the mandatory histopathological tissue diagnosis.

*5.2.2 **Computerised tomography***

Contrast enhanced computerised tomography (CECT) is the most sensitive means to evaluate the thorax, abdomen, and pelvis for TC staging [43]. Contrast enhanced computerised tomography is recommended in all patients for staging before orchidectomy but may be postponed until histopathological confirmation of malignancy.

The size of metastases should be described in three dimensions, or at least by the greatest axial diameter. For abdominal staging, a recent systematic review reports a median sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with CECT of 67% (range 37-100%), 92% (range 58-100%), 87% (60-100%), 73% (67-100%) and 83% (range 71-100%), respectively [43].

Sensitivity decreases and specificity increases with increasing lymph node cut-off size. With nodes ≥ 4 mm pooled sensitivity and specificity are 93% and 58% respectively, whereas for nodes ≥ 10 mm sensitivity is 37% and specificity increases to 100% [43]. Using a 10 mm short-axis lymph node diameter as a cut-off yielded a high specificity (97%), a moderate sensitivity (59%) and false-negative rate of 20% in the retroperitoneum [44]. The expected patterns of nodal spread in TC should be considered when evaluating small and borderline nodes.

Chest CT was evaluated in three studies in a systematic review by Pierorazio *et al.,* [43]. This presents a median sensitivity, specificity, PPV, NPV and accuracy of 100% (range 95-100%), 93% (range 89-97%), 68% (range 25-84%), 100% (range 99-100%) and 93% (range 91-97%), respectively. Computerised tomography of the chest is more sensitive but less specific than chest X-ray (CXR) in thoracic staging. Nevertheless, potential harms of chest CT imaging in low-stage seminoma should be taken into consideration [43].

In patients with masses (< 2 cm) in the retroperitoneum or chest and negative tumour markers, restaging after six to eight weeks rather than treatment initiation is advisable (See sections 7.2.2.1 and 7.2.2.2).

Cerebral imaging by CECT is recommended in patients with NSGCT, multiple lung metastases and poor-prognosis IGCCCG risk group (for patients with hCG values > 5,000 UI/L), or if clinical symptoms are present [45].

5.2.3 *Magnetic resonance imaging*

Magnetic resonance imaging (MRI) of the scrotum provides higher sensitivity and specificity than scrotal US in the diagnosis of TC, but its high cost does not justify its routine use for this purpose [46-48], It should only be considered when US is inconclusive, as local staging for testis-sparing surgery (TSS) planning, to differentiate between paratesticular and intratesticular lesions and/or to characterise intratesticular masses (e.g., distinctive features of Leydig tumours) [46, 47, 49].

Magnetic resonance imaging of the abdomen may be used for staging in case of allergy to iodine-based contrast media with similar accuracy to CECT in the detection of retroperitoneal nodal enlargement [43].

There is no literature regarding the comparative accuracy of CECT and MRI for the detection and evaluation of cerebral metastases in CGTs. Data from cerebral metastasis detection in other malignancies suggest that MRI is far more sensitive than CECT but requires specific expertise [42, 50, 51]. Therefore, when available, MRI should be preferentially used in the evaluation of cerebral metastases in GCTs [51]. Magnetic resonance imaging of the spine is also advisable in patients with symptoms suggesting metastatic disease or if there is equivocal staging on CECT [50].

5.2.4 *Fluorodeoxyglucose-positron emission tomography*

There is no evidence to support the use of Fluorodeoxyglucose-positron emission tomography (FDG-PET) for initial staging and follow-up of TC [43, 50, 52, 53]. Fluorodeoxyglucose-positron emission tomography is only recommended for seminoma patients with post-chemotherapy residual masses > 3 cm (largest diameter) to assess FDG activity [54]. Fluorodeoxyglucose-positron emission tomography should not be performed until at least two months after completion of the last cycle of chemotherapy, as inflammation and the desmoplastic reaction induced by chemotherapy may result in FDG avidity and a false positive result [53]. Whilst the NPV for active disease is > 90% [55, 56], the PPV ranges from 23% to 69% [55-57]. False positives are common and may occur in up to 80% of lesions [55, 57], indicating that necrosis, fibrosis, and the consequent inflammation are also associated with FDG activity. Caution is advised on initiating active therapy driven only by positive findings on FDG-PET-CT [57].

5.2.5 *Bone scan*

There is no evidence to support the use of bone scan for staging of TC.

5.3 Serum tumour markers

5.3.1 *Pre-operative serum tumour markers*

Alphafetoprotein beta subunit of human Chorionic Gonadotropin (β-hCG) and LDH should be determined before and after orchidectomy as they support the diagnosis of TC, may be indicative of GCT histology and are used for disease staging and risk stratification (Table 4.3), as well as to monitor treatment response and detect disease relapse [58, 59].

In a recently reported cohort, the three markers (AFP, β-hCG and LDH) are simultaneously elevated in 7.1% of patients. The elevation of any of these three markers is seen in up to 60% of patients at diagnosis [50.2% (44-56%) in CS I and 93% in CS III (75.8-98.8%)] [59].

Both alphafetoprotein and β-hCG increase is detected in 39% of patients with NSGCT [59], and up to 90% of NSGCTs present with a rise in either AFP or β-hCG at diagnosis [33, 59, 60]. Pure seminomas may also have modestly elevated β-hCG level at diagnosis in up to 30% (9-32%) of cases [58, 59].

Tumour markers have limitations due to their low sensitivity as normal levels do not exclude the presence of disease [60].

5.3.2 *Serum tumour markers after orchidectomy*

Serum levels of AFP, β-hCG and LDH following orchidectomy provide staging and prognostic information [61]. As the serum half-life of AFP and β-hCG are five to seven days and one to three days respectively, it may take several weeks until normalisation occurs [58, 60]. The persistence of, or increase in, serum tumour marker elevation following orchidectomy indicates the likely presence of metastatic disease [59]. Whilst normalisation of marker levels after orchidectomy is a favourable indicator, it does not exclude the possibility of metastatic disease. With metastatic TC, risk stratification is based on serum tumour marker levels immediately before initiation of systemic treatment [61]. Before chemotherapy AFP and LDH levels may act as prognostic factors for OS in non-seminoma intermediate risk group [62].

At relapse, only 25% of patients have elevated AFP and β-hCG, and LDH may remain persistently elevated in 30% of patients despite cure [59]. Tumour markers should be routinely used for follow-up as indicators of recurrence, although the precise frequency of testing is not well defined [63].

*5.3.3 **Other tumour markers***

Micro RNAs (miRNAs) are emerging as potential new biomarkers for TC. A number of studies suggest higher discriminatory accuracy for miRNAs (particularly miR-371a-3p) compared to conventional GCT markers in diagnosis, treatment monitoring, and predicting of residual or recurrent viable disease [64-71]. Furthermore, they may differentiate between GCT and other (stromal/non-germ cell originated) tumours [71]. However, before miRNAs can be considered for use in routine clinical practice, several issues including laboratory standardisation, availability of the test and, importantly, prognostic validation [70] need to be resolved.

5.4 Inguinal exploration and initial management

*5.4.1 **Orchidectomy***

Orchidectomy including division of the spermatic cord at the internal inguinal ring represents the standard of care in patients with TC. Scrotal approach should be avoided when TC is suspected as it results in a higher local recurrence rate [72].

*5.4.2 **Testis-sparing surgery***

Testis-sparing surgery is a valid treatment option in men with interstitial cell or benign testicular tumours and may prevent hypogonadism, lifelong testosterone supplementation and infertility in young men.

In men with TGCTs orchiectomy represents the standard of care as pathological studies describe multifocal and/or adjacent GCNIS in 20-30% of patients [73, 74]. However, TSS when feasible, is indicated in synchronous bilateral tumours or in tumours in solitary testis [75]. Importantly, when indicated in this setting, besides enucleation of the testicular lesion, at least two additional testicular biopsies should be taken to exclude GCNIS [76].

Testis-sparing surgery can also be offered in cases of small or indeterminate testicular masses with negative tumour markers in the presence of a normal contralateral testis in order to avoid the over-treatment of potentially benign lesions and to preserve testicular function [75, 77].

Patients should be informed that cancer can be present even in small (i.e., < 1 cm) masses [75, 78, 79], thus obtaining histology is mandatory.

In both settings, TSS should only be offered together with frozen section examination (FSE). Frozen section examination has shown to be reliable and highly concordant with final histopathology, with a 99% and 96% of sensitivity and specificity respectively and 98% and 97% of PPV and NPV, respectively [77, 80, 81]. In cases of discordance between FSE and final pathology delayed orchiectomy might be needed.

Whether history of GCT or indeterminate small testicular lesion, patients should be made aware on the following issues regarding TSS practice: that limited data exists regarding oncological safety of TSS; that local recurrence rates have been reported (overall 0-26.9%), when TC is present in the specimen [75, 79, 82] and that TSS has implications for ongoing surveillance of the testis. Similarly, patients should be informed about the role and impact of adjuvant radiotherapy when GCNIS is present, on the potential infertility, the need for hormonal supplementation despite parenchyma preservation [75, 79, 83], and that possible discordance between FSE and final pathology may drive the need for a delayed orchidectomy.

*5.4.3 **Insertion of testicular prosthesis***

Testicular prosthesis should be offered to all patients receiving unilateral or bilateral orchidectomy [83]. The prosthesis can be inserted at orchidectomy or subsequently without adverse consequences, including infection [84].

*5.4.4 **Contralateral biopsy***

Contralateral biopsy has been advocated to exclude the presence of GCNIS [85]. Whilst routine policy in some countries [86], the low incidence of GCNIS and metachronous contralateral testicular tumours (up to 9% and approximately 2.5%, respectively) [87, 88], the morbidity of GCNIS treatment (see section 7.1.1), and the fact that most metachronous tumours are low stage at presentation, makes it controversial to recommend routine contralateral biopsy in all patients [89, 90]. Nevertheless, the risks and benefits of biopsy of the contralateral testis should be discussed with TC patients at high risk for contralateral GCNIS, i.e., testicular volume < 12 mL,

and/or a history of cryptorchidism. Contralateral biopsy is not necessary in patients older than 40 years without risk factors [76, 91, 92]. Patients should be informed that a subsequent TGCT may arise despite a negative biopsy [93]. When indicated, a two-site surgical testicular biopsy is the technical procedure recommended [76].

5.5 Pathological examination of the testis

The recommendations for reporting and handling the pathological examination of a testis neoplasm are based on the recommendations of the International Society of Urological Pathology (ISUP) [94-97].

Mandatory pathological requirements:

- *Macroscopic features:* It must indicate radical or partial orchidectomy, side, testis size, number of tumours, and macroscopic features of the epididymis, cord length, and tunica vaginalis.
- *Sampling:* At least a 1 cm^2 section for every centimetre of maximum tumour diameter including normal macroscopic parenchyma (if present), tunica albuginea and epididymis, with selection of suspicious areas. If the tumour is < 20 mm it should be completely sampled.
- At least one proximal (base of the cord) and one distal section of spermatic cord plus any suspicious area. Cord blocks should preferably be taken prior to tumour sections to avoid contamination.
- *Microscopic features and diagnosis:* histological types (specify individual components and estimate amount as percentage) according to WHO 2016 [94]:
  - Presence or absence of peri-tumoural lymph vessels and/or blood vessels invasion. In case of doubt, the use of endothelial markers, such as CD31, are recommended.
  - Presence or absence of GCNIS in non-tumour parenchyma.
  - In case of rete testis invasion attention should be paid to distinguishing between pagetoid involvement and stromal invasion [95].
- If microscopic findings are not concordant with serum markers further block samples should be taken.
- pT category according to TNM 2016 [27]. In a multifocal seminoma the largest nodule should be used to determinate pT category.

Immune-histochemical markers in cases of doubt are:

- Seminoma: CD-117 (c-KIT), OCT 3/4, Sall4, PLAP
- GCNIS: CD-117 (c-KIT), OCT 3 / 4, Sall4, PLAP
- Syncytiotrophoblast: β-hCG
- Embryonal carcinoma: CD30
- Yolk sac tumour: Glypican 3
- Sex cord gonadal tumours: Inhibin, calretinin

The search for i12p (FISH or PCR) or gain in Ch9 (spermatocytic tumour) are additional immuno-chemistry techniques, utility confirmation of other molecular markers such as P53, MDM2, KRAS AND HRAS is awaited [98].

In order to facilitate consistent and accurate data collection, promote research, and improve patient care, the International Collaboration on Cancer Reporting has constructed a dataset for the reporting of urological neoplasms. The dataset for testicular tumours encompasses the updated 2016 WHO classification of urological tumours, the ISUP consultation and staging with the 8th edition of the American Joint Cancer Committee (AJCC) [97].

The dataset includes those elements unanimously agreed by the expert panel as “required” (mandatory) and those “recommended” (non-mandatory) that would ideally be included but are either non-validated or not regularly used in patient management [97]. The dataset for handling pathological assessment of TC is shown in Table 5.5.

Table 5.5: Recommended dataset for reporting of neoplasia of the testis (modified from the International Collaboration on Cancer Reporting) [97].

Elements	Required	Recommended*	Content	Remarks
Clinical information		√	- Not provided - Previous history of testicular cancer - Previous therapy - Other	Specify each
Serum tumour markers		√	- Not provided - If provided within normal limits or - Specify serum tumour markers used - Specify levels - Specify date markers were drawn	Select all that apply: Serum tumour markers: LDH (IU/L), AFP (ug/L), β-hCG (IU/L)
Operative procedure	√		- Not specified - Orchidectomy partial - Orchidectomy radical - Other	Specify side for partial or radical orchidectomy. Specify other
Tumour focality	√		- Cannot be assessed - Indeterminate - Unifocal - Multifocal	If multifocal specify number of tumours in specimen.
Maximum tumour dimension	√		- Cannot be assessed - Dimensions largest tumour (mm) - Dimensions additional tumour nodules[#]	Specify at least maximum diameter of largest tumour. Preferably specified 3 dimensions/axes.[#]
Macroscopic extent of invasion	√		- Cannot be assessed - Confined to testis - Invades epididymis - Invades tunica vaginalis - Invades hilar structures - Invades spermatic cord - Invades scrotum - Other	Select all that apply. If other specify.
Block identification key		√	N/A	List overleaf or separately with indication of nature and origin of all tissue blocks.
Histological tumour type	√		- Germ cell tumour: type and percentage - Other	Use WHO classification (2016). If other specify.
Microscopic extent of invasion	√		- Rete testis of stromal/ interstitial type - Epididymis - Hilar fat - Tunica albuginea[#] - Tunica vaginalis - Spermatic cord - Scrotal wall	For all: - not submitted - not involved - involved
Lymphovascular extension	√		- Not identified - Present	If present specify type.[#]
Intratubular lesions (GCNIS)	√		- Not identified - Present - Other intratubular lesions[#]	If other intratubular lesions present identify type.[#]

Margin status	√		- Partial orchidectomy: . cannot be assessed . involved . not involved - Radical orchidectomy: . cannot be assessed . spermatic cord margin involved . spermatic cord margin not involved - Other margin involved	In partial orchidectomy if margin not involved, distance of tumour from closest margin (mm).# If other margin involved specify.
Coexisting pathology		√	- None identified - Hemosiderin-laden macrophages - Atrophy - Other	If other specify
Ancillary studies		√	- Not performed - Performed	If performed specify
Response to neoadjuvant therapy		√	- Present - Absent, - No prior treatment, - Cannot be assessed	Explain reasons if cannot be assessed.
Pathologic staging*	√		T classification according to TNM 8th edition (UICC)**	m-multiple primary tumours r-recurrent y-post-therapy

* *Not mandatory. Ideally to be included but either non-validated or no regularly used in patient management.*

** *TNM 8th edition (AJCC) used in the original publication.*

\# *Recommended, i.p. intratubular seminoma and embryonal carcinoma.*

5.6 Screening

There are no high-level evidence studies supporting screening programs. It has not been shown that screening asymptomatic patients has benefit in terms of detecting TC at a more curable stage, despite the fact that stage and prognosis have been shown to be directly related to early diagnosis [99, 100].

Until clinical data supporting or refuting self-examination in the general population becomes available, TC patients and their family members should be informed about the importance of physical self-examination, particularly in the presence of clinical risk factors including family history of TC [101].

5.7 Impact on fertility and fertility-associated issues

Sperm abnormalities and Leydig cell dysfunction are frequently found in patients with TCs prior to orchidectomy [102, 103]. Up to 24% of TC patients are azoospermic and almost 50% have abnormal sperm counts (oligozo-ospemic) before treatment [103].

Treatment for TC, including orchidectomy, may have a negative impact on reproductive function [104]. Chemotherapy and radiation treatment (RT) can both impair fertility; although, long-term infertility is rare after radiation therapy and is dose-cumulative-dependent after chemotherapy [105-107]. Spermatogenesis usually recovers one to four years after chemotherapy [108]. In CS I, adjuvant treatment (BEP [cisplatin, etoposide, bleomycin] x1; Carbo x1) does not appear to significantly affect testicular function compared to surveillance, with full recovery after one year [109].

All patients should be offered semen preservation as the most cost-effective strategy for fertility preservation, and pre-treatment fertility assessment (testosterone, luteinising hormone [LH] and follicle stimulating hormone [FSH] levels) is advised [110].

If cryopreservation is desired, sperm banking should be offered before orchidectomy, maximizing the chances of fertilisation, and avoiding the risk of a non-functioning remaining testicle after surgery. If not arranged before orchidectomy, it should be undertaken prior to chemotherapy or RT [105-107, 110, 111].

Long-term testosterone supplementation is necessary in patients who have had bilateral orchidectomy or have low testosterone levels after treatment of GCNIS [112].

Chemotherapy and RT are both teratogenic. Therefore, contraception must be used during treatment and for at least six months after its completion [113].

For more detailed information, the reader is referred to the EAU Guidelines on Sexual Reproductive Health [114].

5.8 Guidelines for the diagnosis and staging of Testicular Cancer

Summary of evidence	LE
Poor sperm quality is frequently found in TC patients, before and after treatment. Semen preservation is the most cost-effective strategy for fertility preservation.	2b
Serum tumour markers (AFP, β-hCG and LDH) should be determined before and after orchidectomy and throughout follow-up. They are used for accurate staging, risk stratification, to monitor treatment and to detect relapse.	2b
For abdominal staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 67%, 95%, 87%, 73% and 83%, respectively. Sensitivity decreases and specificity increases with increasing lymph node size.	2a
For chest staging, CECT has a median sensitivity, specificity, PPV, NPV and accuracy of 100%, 93%, 68%, 100% and 93%, respectively	2a
Contrast enhanced computerised tomography and MRI are key image modalities for the detection of brain metastasis. Magnetic resonance imaging is far more sensitive than CECT, though it does require expertise.	2b
Fluorodeoxyglucose-positron emission tomography has a limited diagnostic accuracy for staging before chemotherapy.	2b
There are no high-level evidence studies supporting screening programs.	2b
In testicular sparing surgery, FSE has shown to be reliable and highly concordant with final histopathology.	1b
There is no evidence supporting any size criteria for a testicular lesion to be safely followed-up.	2b
In patients without risk factors, there is low incidence of contralateral GCNIS and of metachronous GCTC.	2b

Recommendations	Strength rating
Discuss sperm banking with all men prior to starting treatment for testicular cancer (TC).	Strong
Perform bilateral testicular ultrasound (US) in all patients with suspicion of TC.	Strong
Perform physical examination including supraclavicular, cervical, axillary, and inguinal lymph nodes, breast, and testicles.	Strong
Measure serum tumour markers both before and after orchidectomy taking into account half-life kinetics.	Strong
Perform orchidectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, commence chemotherapy prior to orchidectomy.	Strong
Perform contrast enhanced computerised tomography (CECT) scan (chest, abdomen, and pelvis) in patients with a diagnosis of TC. In case of iodine allergy or other limiting factors perform abdominal and pelvic magnetic resonance imaging (MRI).	Strong
Perform MRI of the brain (or brain CECT if not available) in patients with multiple lung metastases, or high beta subunit of human Chorionic Gonadotropin (β-hCG) values, or those in the poor-prognosis International Germ Cell Cancer Collaborative Group (IGCCCG) risk group.	Strong
Do not use positron emission tomography–computed tomography or bone scan for staging.	Strong
Encourage patients with TC to perform self-examination and to inform first-degree male relatives of the need for self-examination.	Weak
Discuss testis-sparing surgery with frozen section examination in patients with a high likelihood of having a benign testicular tumour which are suitable for enucleation.	Strong
Discuss biopsy of the contralateral testis to patients with TC and who are at high-risk for contralateral germ cell neoplasia "*in situ*".	Strong

6. PROGNOSIS

6.1 Risk factors for metastatic relapse in clinical stage I testicular cancer

With stage I seminoma, primary testicular tumour size and stromal invasion of the rete testis have been identified as predictors for relapse in a pooled analysis of retrospective data [115]. Absence of both factors indicates a low risk of recurrence (6%) [116]. Whilst the original analysis was not supported by a further retrospective report [117], some prospective series [118-120] support the prognostic significance of tumour size and stromal invasion of the rete testis. Two systematic reviews have assessed the prognostic value of these risk factors [121, 122]. While tumour size (continuous or dichotomised) and rete testis invasion are associated with a higher risk of relapse, both systematic reviews highlighted the low quality of the studies included and that the level of evidence is too low to recommend the use of these pathological risk factors to drive adjuvant treatment decisions [121, 122].

For non-seminoma stage I, invasion of the primary tumour into blood or lymphatic vessels, lymphovascular invasion (LVI), is the most reliable single predictor of occult metastatic disease [96, 123, 124]; while interobserver agreement is limited, immunohistochemistry might improve detection [125]. The percentage of embryonal carcinoma within a tumour may enhance the PPV and NPV of LVI [123], but there is no definitive prognostic cut-off for percentage [123]. Risk of relapse at five years with LVI is 50% compared to 15% without LVI. The significant prognostic pathological risk factors for stage I TC are listed in Table 6.1.

Table 6.1: Pathological risk factors for occult metastatic disease in stage I testicular cancer

Histological type	**Seminoma** [121]	**Non-seminoma** [95, 124]
• Pathological risk factors	• Tumour size • Invasion of the rete testis	• Lympho-vascular invasion in peri-tumoral tissue

7. DISEASE MANAGEMENT

The availability of cis-platin based chemotherapy to which TC is exquisitely sensitive, in combination with surgery and in highly selected cases, radiotherapy, has resulted in the high cure rates seen with this disease [126]. Careful staging at diagnosis, adequate early treatment based on a multidisciplinary approach, rigorous follow-up and adequate initiation of salvage therapies are critical to successful outcomes.

Whilst early stages can be successfully treated in a non-specialist centre, relapse rates are higher than in specialist centres [127, 128]. In clinical trials on poor-prognosis patients, OS relates to the number of patients treated at the participating centre (worse if < 5 patients enrolled) [129]. Treatment at high-volume specialist centres is thus strongly encouraged. Establishment of second-opinion clinics for TC patients as well as collaboratively working with specialist centres may also help prevent over- and under-treatment [130]. This will ensure that patients are neither subjected to unnecessary or inappropriate treatment and associated toxicities or denied early management options which may subsequently compromise their long-term quality of life or survival.

Initiation of treatment before histopathological confirmation:
In cases of life-threatening disseminated disease, chemotherapy should commence immediately, particularly when the clinical picture strongly supports TC, and/or tumour markers are increased. Orchidectomy in these circumstances can be delayed until clinical stabilisation occurs or subsequently be performed in combination with resection of residual lesions.

7.1 Stage I germ cell tumours

7.1.1 Germ cell neoplasia "in situ" (GCNIS)

If GCNIS is diagnosed in a patient with a solitary testis, local radiotherapy (18-20 Gy in fractions of 2 Gy) should be considered [107, 131-133]. Chemotherapy is significantly less effective, and the cure rates are dose-dependent [131]. Radiotherapy to a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency [107]. Fertile patients who wish to father children may delay radiation therapy and be monitored with regular testicular US [76].

If GCNIS is diagnosed and the contralateral testis is normal, management options include orchidectomy or close observation, as the five-year risk of developing TC is 50% [134].

7.1.2 ***Seminoma germ cell tumour clinical stage I (SGCT CS I)***

Approximately 15% of clinical stage I SGCT patients have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchidectomy alone [117, 120, 135, 136]. Adjuvant treatment decisions should be based on thorough discussions with the patient, incorporating potential advantages and disadvantages, as well as individual patient circumstances.

7.1.2.1 Surveillance

Several prospective non-randomised surveillance studies have been conducted over the past decade. These have shown an overall risk of relapse in unselected CS I patients of 12-20% at five years with 17% in the largest series of over 1,500 patients [137]. Most occur in the retroperitoneal lymph nodes during the first two years [138-140].

Risk of relapse is 12% with small size (tumours < 3 cm) as a single parameter [119, 139]. With both small tumour size (< 4 cm) and absence of stromal rete testis invasion even lower recurrence rates of 6% have been described.

The cancer-specific survival (CSS) rate reported with surveillance for CS I seminoma performed by specialist centres is over 99% [137, 138, 140, 141]. Whilst cost effective compared to other management strategies [142], surveillance can represent a burden to the patient due to the need for repeated imaging of the retroperitoneum and clinic visits. These may impact patient compliance which is crucial to an active surveillance strategy.

7.1.2.2 Adjuvant chemotherapy

A trial compared one cycle of carboplatin reaching area under curve of 7 mg/mL/min (AUC 7) with adjuvant RT. This showed no difference in relapse free rates (95% and 96%), time to recurrence and survival after a median follow-up of four years [143-145]. Non-randomised risk-adapted population-based studies using one cycle of carboplatin reported a lower five-year relapse rate of 3%-4% compared to 14-16% with active surveillance [138, 140]. Adjuvant carboplatin (AUC 7) is therefore an alternative to RT or surveillance in CS I seminoma [138, 143, 144]. Retrospective data shows a median time to relapse after Carboplatin of nineteen months , with 15% of relapses occurring beyond three years. Time to relapse after after Carboplatin is longer than with active surveillance. Most patients relapsing after adjuvant carboplatin can be successfully treated with a standard cisplatin-based chemotherapy regimen appropriate to their disease stage [146].

7.1.2.3 Adjuvant radiotherapy

Seminomas are extremely radiosensitive tumours. Adjuvant RT to a para-aortic (PA) field or a PA and ipsilateral field (PA and ipsilateral iliac nodes), with a total dose of 20-24 Gy, reduces the relapse rate between 1-3% [147-149]. A large MRC RCT of 20 Gy vs. 30 Gy PA radiation in CS I seminoma showed non-inferiority in terms of recurrence rates [148]. A scrotal shield should be considered during adjuvant RT in order to prevent scattered radiation toxicity in the contralateral testis [150]. Adjuvant irradiation of supra-diaphragmatic lymph nodes is not indicated.

Whilst moderate acute gastrointestinal side effects occur in up to 60% of patients, moderate chronic gastrointestinal side-effects are present in about 5% of patients. Severe radiation induced long-term toxicity is seen in less than 2% of patients.

The main concern with adjuvant RT is the long-term risk of radiation-induced non-germ cell malignancies [150-153]. This has limited its role in CS I seminoma to elderly patients and those unfit for chemotherapy.

7.1.2.4 Risk-adapted treatment

Tumour size > 4 cm and stromal rete testis invasion may stratify patients into low- and high-risk groups. These risk factors were introduced based on an analysis of retrospective trials [102], and then confirmed in subsequent prospective studies [119, 120]. Patients with both risk factors have a 32% of relapse compared to 6% with neither. Prospective trials based on these risk factors have demonstrated the feasibility of a risk-adapted approach to CS I seminoma.

A large study in 744 patients with CS I seminoma managed with a risk-adapted policy (low risk [0-1 factors] receiving active surveillance and high risk [1-2 factors] treated with two adjuvant courses of carboplatin, AUC 7) with a median follow-up of 67 months showed 12% of low-risk cases relapsed on active surveillance

whilst 3% of those with one or both risk factors relapsed with adjuvant chemotherapy. The patterns and outcome of relapse was similar in the two groups [119, 154].

A trial of 897 patients offered surveillance to patients with no or one risk factor whilst patients with both risk factors were offered one dose of carboplatin, AUC 7 [120]. The decision regarding adjuvant treatment was made by the individual patient. At a median follow-up of 5.6 years, patients without risk factors had a relapse rate of 4% with surveillance compared to 2% with adjuvant carboplatin. When one or both risk factors were present, 15.5% of surveillance patients relapsed whereas 9% receiving adjuvant carboplatin relapsed. Thirty-three per cent of relapses who received adjuvant carboplatin occurred more than three years after orchidectomy with 3% occurring after five years [120].

7.1.2.5 Guidelines for the treatment of clinical stage I seminoma testis tumours

Summary of evidence	**LE**
Primary testicular tumour size and stromal rete testis invasion correlate with the risk of relapse. The evidence to guide adjuvant treatment decisions is, however, too limited to justify its routine use in clinical practice.	2a
Active surveillance is a feasible approach with conditional relapse risk in unselected series of between 12% and 20%.	2a
In patients without risk factors the five-year relapse rate under surveillance is 4-6%, whereas in the presence of one or two risk factors, five-year relapse rate in contemporary surveillance series is 15-20%.	2b
In non-randomised prospective series five-year relapse rates with adjuvant carboplatin are 2% in patients without risk factors and 9% in patients with one or both risk factors.	2b
Adjuvant chemotherapy with one course carboplatin AUC 7 is not inferior to adjuvant radiotherapy when pathological risk factors are considered. Relapse rates with both adjuvant treatments are around 5%.	1b
Adjuvant radiotherapy is associated with an increased risk of developing secondary non-germ cell malignancies.	2b

Recommendations	**Strength rating**
Fully inform the patient about all available management options, including surveillance or adjuvant therapy after orchidectomy, as well as treatment-specific recurrence rates and acute and long-term side effects.	Strong
Offer surveillance as the preferred management option if resources are available and the patient is compliant.	Strong
Offer one dose of carboplatin at area under curve (AUC) 7 if adjuvant chemotherapy is considered.	Strong
Do not perform adjuvant treatment in patients at very low-risk of recurrence (no risk factors).	Strong
Do not routinely perform adjuvant radiotherapy.	Strong
Adjuvant radiotherapy should be reserved only for highly selected patients not suitable for surveillance and with contraindication for chemotherapy.	Strong

*7.1.3 **Non-seminomatous germ cell tumours clinical stage I (CS I-NSGCT)***

Management options for CS I-NSGCTs comprise surveillance, adjuvant chemotherapy or retroperitoneal lymph node dissection. Overall, approximately 70% of CS I-NSGCTs are cured with orchiectomy alone. In those with the high-risk feature of LVI, relapse occurs in 50% compared to 15% in those without LVI. A thorough discussion should be undertaken with the patient outlining the potential advantages and disadvantages of treatment options, as well as individual co-morbidities, disease features, risk factors, specific circumstances, and personal preferences, to guide their treatment decision.

7.1.3.1 Surveillance

Surveillance for CS I-NSGCT entails a strict protocol of repeated cross-sectional imaging, monitoring of serum tumour markers and clinical assessment for the early identification of the subset of patients experiencing relapse who must receive salvage treatment.

The largest reports of surveillance indicate a cumulative relapse risk in about 30% of CS I-NSGCT (five-year conditional risk of relapse 42% and 17% for high- and low-risk CS I-NSGCT, respectively) [136, 137]. Of these, 92% present within the first two years [136, 137].

Serum tumour markers alone are an unreliable indicator of relapse. In a systematic review of CS I-NSGCT patients undergoing surveillance, the rate of marker elevation at time of relapse varied between 28 and 75% [155]. Approximately 60% of relapses occur in the retroperitoneum and 11% have large volume metastatic recurrent disease reinforcing the need for cross-sectional imaging [136, 156].

Surveillance studies have reported lower relapse rates compared to some series of patients undergoing primary Retroperitoneal lymph node dissection (RPLND) [157]. This is likely related to both selection bias with both exclusion of high-risk cases and very early marker relapse precipitating treatment prior to surveillance re-imaging. Based on the overall CSS data, surveillance within a rigorous protocol can safely be offered to patients with non-risk stratified CS I-NSGCT who are compliant and informed about the expected recurrence rate and need for salvage treatment [156, 158, 159].

7.1.3.2 Retroperitoneal lymph node dissection (RPLND)

Prior to the availability of effective systemic therapy for relapsed disease primary RPLND for CS I-NSGCT evolved as a strategy which improved survival following orchidectomy [160]. A large series of 464 unselected cases of CS I-NSGCT commencing within this era reported an overall relapse rate of 14%. Of PS (pathological stage) II cases 36% relapsed. With PS I cases 11% relapsed – which is consistent with more contemporary series reporting approximately 10% of patients with no evidence of nodal involvement at RPLND (i.e., PS I) relapsing at distant sites [123, 160, 161]. More recent series report lower relapse rates possibly reflecting case selection [162].

Since the introduction of platin based chemotherapy the role of adjuvant primary RPLND in men with stage I GCT has decreased. The few indications in stage I disease include men with Teratoma with somatic malignant transformation, interstitial cell tumours with an increased risk of metastases or patients who are not willing or suitable to undergo chemotherapy in case of a later recurrence.

With RPLND 18-30% of patients have active nodal malignancy (i.e., PS II), [161, 163]. Without further treatment approximately 30% of these will recur [161]. The presence of LVI, predominant embryonal carcinoma and pT stage of the primary as well as histologically extranodal tumour extension all appear associated with an increased risk of recurrence. The use of these further parameters has yet to be clearly defined in clinical practice [161, 164]. However, following RPLND, presence and extent of lymph-node involvement (specifically lymph-node ratio), may represent stronger predictive factors of recurrence and could be adopted for subsequent decision making [161, 162].

Strategies to reduce the morbidity of primary RPLND include nerve-sparing and minimally invasive approaches. In a multicentre setting, higher rates of in-field recurrences and complications have been reported with nerve-sparing RPLND [163, 165]. This suggests that primary RPLND, when indicated or chosen, should be performed by an experienced surgeon in a specialist centre. Minimally invasive (laparoscopic or robot-assisted) primary RPLND, appears feasible and safe (e.g., low-complication rate) in experienced hands. However, most of the series have only a short follow-up precluding definitive conclusions regarding oncological outcomes when compared to open primary RPLND. At present, it cannot be recommended outside of a high-volume RPLND centres with appropriate minimally-invasive expertise [166-173].

Follow-up after RPLND is less demanding and costly than other options due to the reduced need for cross-sectional imaging [174]. Nevertheless, in view of the high CSS rates of surveillance with salvage treatment in cases of relapse, the low relapse rates with adjuvant chemotherapy, and the lower reproducibility of primary RPLND on a large scale, its role for CS I-NSGCT has diminished.

7.1.3.3 Adjuvant chemotherapy

Adjuvant chemotherapy has been evaluated with both one and two cycles of BEP in CS I-NSGCT. A prospective trial from 1996, as well as subsequent studies, used two cycles of BEP in high-risk patients (LVI present) [175-177]. In these series, including 200 patients, some with a median follow-up of nearly 7.9 years [175], a relapse rate of only 2.7% was reported, with minimal long-term toxicity. Two cycles of cisplatin-based adjuvant chemotherapy also do not seem to adversely affect fertility or sexual activity [178].

More studies have shown one cycle of adjuvant BEP results in similar very low recurrence rates (2-3%) [179, 180]. Reduction from two to one cycle of BEP improves the risk-benefit ratio of adjuvant chemotherapy considerably. A randomised phase III trial has also compared two-year recurrence free survival with adjuvant BEP x 1 to RPLND. Results favoured chemotherapy with recurrence free survival of 99.5% vs. 91% [165]. The hazard ratio to experience a tumour recurrence with surgery compared to BEP x 1 was 8 [165]. No clinically relevant differences in quality of life (QoL) were detected [181].

A community based prospective study of 490 unselected patients with CS I-NSGCT that received adjuvant single cycle BEP had five-year relapse rates of 3% and 2% for LVI+ and LV- patients, respectively. After a median follow-up of eight years these rates were sustained, no relapses were observed beyond 3.3 years [179, 180]. These numbers imply that > 90% of relapses are prevented by single cycle BEP which is now the recommended strategy if adjuvant chemotherapy is considered [179, 180]. The very-long term (> 20 years) side effects of adjuvant chemotherapy, particularly cardiovascular, are yet to be fully defined which should be considered with decision-making [182, 183].

Limited data are available on outcomes with relapse after adjuvant BEP. A retrospective analysis indicated that about one third of these relapses were late and that the outcome may be slightly worse compared to those presenting with *de novo* metastatic disease [184].

7.1.3.4 Risk-adapted treatment

A risk-adapted strategy is an alternative to any single approach for patients with CS I-NSGCT. The advantages and disadvantages of treatment options must be discussed with patients in the context of their specific circumstances including disease risk factors, co-morbidities, and personal preference, as well as clinician recommendation in reaching a treatment decision. Lymphovascular invasion appears as the strongest predictive risk factor for relapse and should be carefully outlined to the patient in order to assist in their decision-making.

Patients without LVI should be guided to consider surveillance, although some patients with significant co-morbidities or concerns regarding salvage chemotherapy with multicycle cisplatin-based chemotherapy may opt for adjuvant therapy. Those with LVI should have their high risk of relapse (up to 50%) highlighted and be guided to consider adjuvant management, and chemotherapy with BEP X 1 as the “preferred” option.

Some patients may wish to consider primary RPLND although they need to be aware of the potential additional requirement of adjuvant chemotherapy if nodes contain active disease (pN1), as well as the 10% risk of systemic relapse, even if pN0, requiring subsequent chemotherapy treatment (BEP X 3).

7.1.3.5 Post Pubertal Teratoma with somatic malignant component

According to a multi-institutional study analysing retrospective datasets of CS I patients with post-pubertal teratoma with somatic malignant component (TSMC), these patients had inferior five-year OS of approximately 10% compared to other CS I-GCT patients. Furthermore, CS I TSMC cases undergoing primary RPPLND had a much higher proportion of nodal metastases (PS II) than expected (37.5%). Despite its limitations this study provides the strongest evidence on this issue and supports primary RPLND in CS I-NSGCT with TSMC [185].

For patients presenting with CS I pure post-pubertal teratoma without a somatic malignant component, surveillance provides comparable survival outcomes to primary RPLND [186]. However, subtype discrepancies in primary diagnostic of post-pubertal teratoma are not infrequent. When present they consist in addition of subtype and involve secondary somatic type of malignancy in 83% of cases. As such, central review by expert genitourinary pathologist is recommended when teratoma is diagnosed in the orchidectomy specimen [187].

7.1.3.6 Guidelines for the treatment of clinical stage I non-seminoma testis

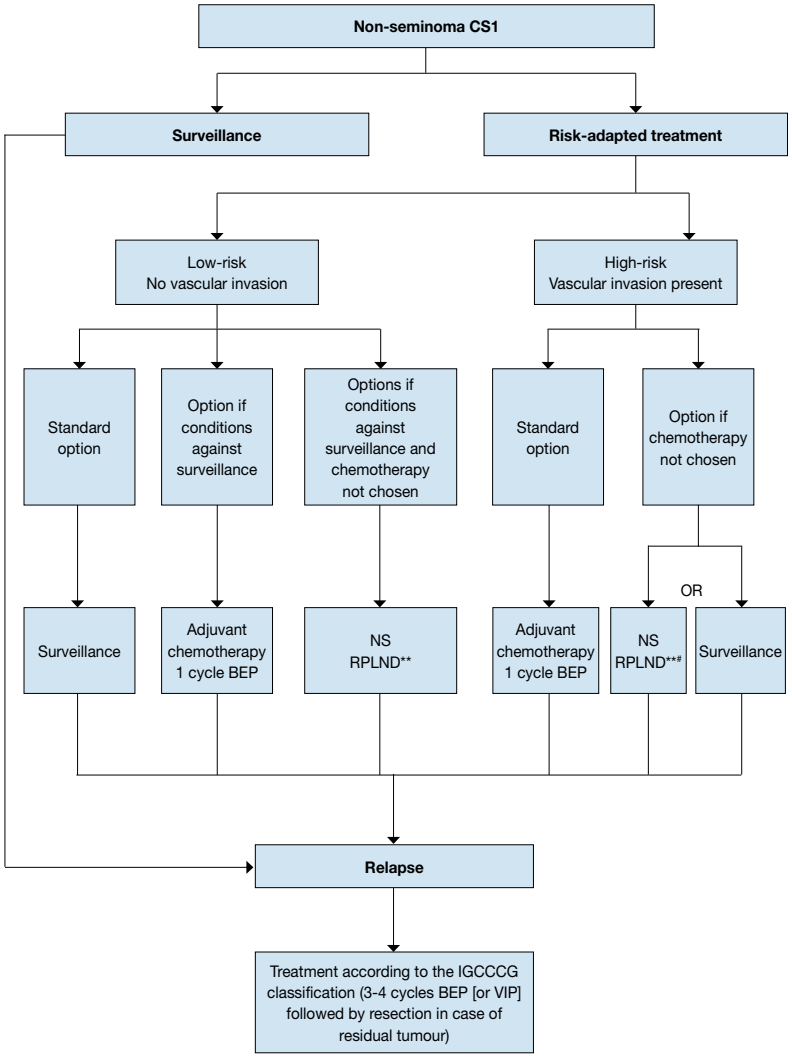
Summary of evidence	**LE**
Lymphovascular invasion increases the risk of relapse.	2a
The relapse rate with active surveillance is up to 50%, depending on LVI status.	2a
The relapse rate in patients who receive adjuvant chemotherapy with BEP (x 1 cycle) is up to 3%.	2a
Adjuvant chemotherapy with BEP is superior to adjuvant RPLND in terms of the risk of relapse.	1b
A risk-adapted approach, based on lymphovascular invasion is feasible.	2b
The acute toxicity of one cycle adjuvant BEP is low.	1b

Recommendations	**Strength rating**
Inform patients about all management options after orchidectomy: surveillance, adjuvant chemotherapy, and retroperitoneal lymph node dissection, including treatment-specific recurrence rates as well as acute and long-term side effects.	Strong
Offer surveillance or risk-adapted treatment based on lymphovascular invasion (see below).	Strong
Discuss one course of cisplatin, etoposide, bleomycin as an adjuvant treatment alternative in patients with stage I non-seminomatous germ cell tumour if patients are not willing to undergo or comply with surveillance.	Strong

7.1.3.7 Risk-adapted treatment for clinical stage I non-seminomatous germ cell tumour based on vascular invasion

Recommendations	Strength rating
Stage IA (pT1, no vascular invasion): low-risk	
Offer surveillance if the patient is willing and able to comply.	Strong
Offer adjuvant chemotherapy with one course of cisplatin, etoposide, bleomycin (BEP) in low-risk patients not willing (or unsuitable) to undergo surveillance.	Strong
Stage IB (pT2-pT4): high-risk	
Offer adjuvant chemotherapy with one course of BEP, or surveillance and discuss the advantages and disadvantages.	Strong
Offer surveillance to patients not willing to undergo adjuvant chemotherapy.	Strong
Offer nerve-sparing retroperitoneal lymph node dissection to highly selected patients only; those with contraindication to adjuvant chemotherapy and unwilling to accept surveillance.	Strong
Primary retroperitoneal lymph node dissection should be advised in men with post-pubertal teratoma with somatic malignant component.	Weak

Figure 1: Risk-adapted treatment in patients with clinical stage I non-seminoma NSGCT [188]*



** Discuss all treatment options with individual patients, to allow them to make an informed decision as to their further care.*

*** In case of PS II, the rate of recurrence is higher and chemotherapy can be administered (max. 2 cycles).*

Primary retroperitoneal lymph node dissection should be advised in men with post-pubertal teratoma with somatic malignant component.

BEP = cisplatin, etoposide, bleomycin; CS = clinical stage; IGCCCG = International Germ Cell Cancer Collaborative Group; NS = nerve-sparing; RLNPD = retroperitoneal lymph node dissection; VIP = etoposide, cisplatin, ifosfamide.

7.2 Metastatic germ cell tumours

The first-line treatment of metastatic GCTs depends on:

- the histology of the primary tumour;
- prognostic groups as defined by the IGCCCG (Table 4.3) [61];
- serum tumour marker decline during the first cycle of chemotherapy in poor-prognosis patients.

In relapsed patients, a prognostic score has been developed including response to first-line therapy which can be used to estimate patient outcome following salvage chemotherapy [189].

*7.2.1 **Clinical stage I with (persistently) elevated serum tumour markers***

If AFP or β-hCG increase or fail to normalise following orchidectomy, US examination of the contralateral testicle must be performed. If a contralateral tumour is excluded, repeat staging four weeks after orchidectomy is required [188].

Some patients may have stable but slightly elevated AFP or β-HCG and can be initially monitored. Treatment should be commenced if markers rise or when follow-up imaging demonstrates metastatic disease [188].

The treatment of true CS IS-NSGT should be the same as other good-prognosis metastatic non-seminoma (stage IIA/B). With this, five- and ten-year disease-free survival of 87% and 85%, respectively, have been recently reported [190].

*7.2.2 **Metastatic disease (stage IIA/B)***

7.2.2.1 Stage IIA/B seminoma

Patients with enlarged retroperitoneal lymph nodes < 2 cm and normal markers may be observed for six to eight weeks with repeat-staging imaging as these may be non-metastatic. Treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise [188, 190]. A special case are those patients who can undergo primary RPLND within a trial or institutional study (see below for further details).

Standard historical treatment of stage II A/B seminoma has been radiotherapy, with reported relapse rates of 9-24% [191, 192]. Most reports describe large target fields and high doses. Further studies using more limited fields report similar rates of relapse [193]. The radiation dose recommended in stage IIA and IIB is 30 Gy and 36 Gy, respectively, with the standard field encompassing the PA and ipsilateral iliac nodes. With these, five-year relapse-free survival rates in stage IIA and IIB are 92% and 90%, respectively [191, 192]. Further dose reduction in stage IIA to 27 Gy is associated with a higher relapse rate of 11% [140, 193].

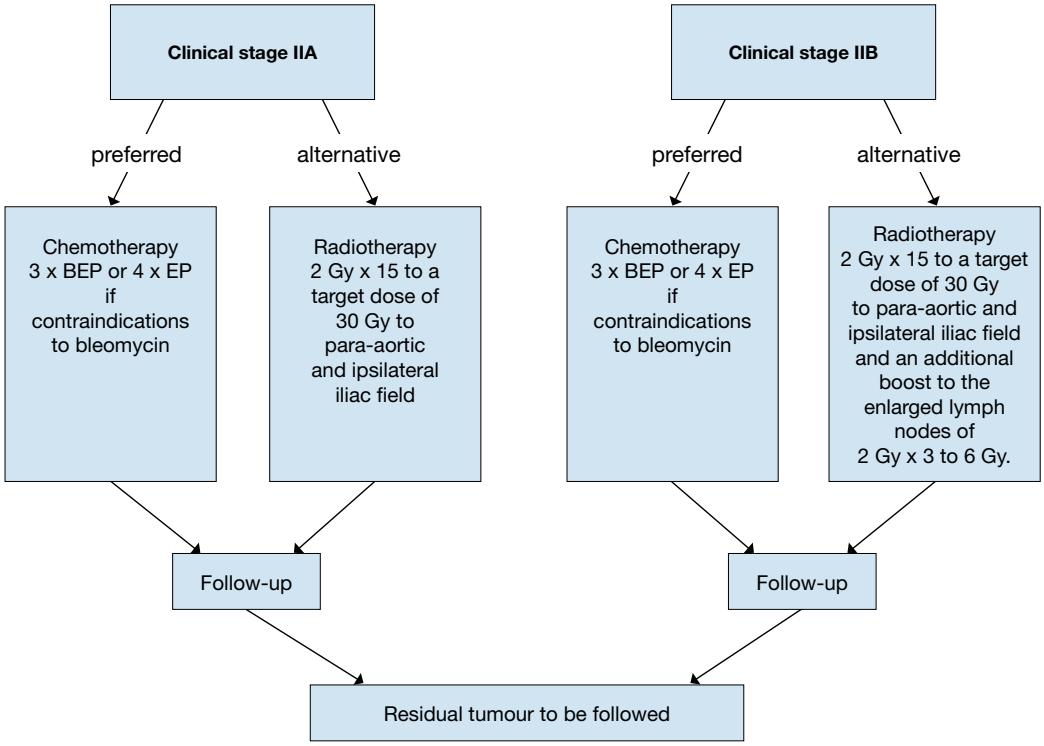
Accumulating data on long-term morbidity, such as an increased risk of cardiovascular events and second malignancies following radiotherapy has raised concerns. One study with a follow-up of nineteen years reported a sevenfold higher all-cause mortality rate than mortality due to seminoma [194].

Currently, chemotherapy is the preferred alternative to radiotherapy for stage II seminoma. This entails three cycles of BEP as a preferred strategy, or four cycles of etoposide and cisplatin (EP) as an alternative in case of contraindications to bleomycin, or for older patients [195]. There are no randomised studies comparing radiotherapy and chemotherapy. A recent meta-analysis of thirteen high-quality studies, comparing efficacy and toxicity of radiotherapy and chemotherapy in stage IIA/IIB patients [196], showed that radiotherapy and chemotherapy appeared to be similarly effective in both stages, with a non-significant trend towards greater efficacy for chemotherapy (HR: 2.17) in stage IIB seminoma [196]. Acute toxicity was almost exclusively reported following chemotherapy, while long-term toxicity was more frequent following radiotherapy, mainly comprising bowel toxicity and secondary cancers, generally in the irradiated field [196]. Radiation therapy may be considered in highly selected patients who are either elderly or have contraindications or difficulties tolerating systemic chemotherapy.

Single agent carboplatin, using three to four cycles at AUC 7 is not an alternative to standard EP or BEP chemotherapy for metastatic disease, due to the risk of failure (19%) or subsequent relapse (13%) at the site of initial nodal disease [197]. The same strategy utilising a higher dose of carboplatin, AUC 10, has also been reported in a trial [198] and a subsequent multi-institutional analysis [199]. The latter study comprised 216 patients and reported three-year PFS of 96.5% and five-year DSS of 98.3% comparable to standard regimens. Myelosuppression was the principal toxicity with 37% and 27% experiencing grade 3 or higher neutropenia and thrombocytopenia, respectively.

Primary RPLND has also been reported for CS II seminoma [200, 201]. Data from the National Cancer Data Base identified 155 men who underwent primary RPLND for CS II A/B reporting five-year OS of 92%. Specific trials are addressing the role of primary RPLND compared to standard options.

Figure 2: Treatment options in patients with seminoma clinical stage IIA and B*


Clinical stage IIA
Clinical stage IIB
preferred
alternative
preferred
alternative
Chemotherapy 3 x BEP or 4 x EP if contraindications to bleomycin
Radiotherapy 2 Gy x 15 to a target dose of 30 Gy to para-aortic and ipsilateral iliac field
Chemotherapy 3 x BEP or 4 x EP if contraindications to bleomycin
Radiotherapy 2 Gy x 15 to a target dose of 30 Gy to para-aortic and ipsilateral iliac field and an additional boost to the enlarged lymph nodes of 2 Gy x 3 to 6 Gy.
Follow-up
Follow-up
Residual tumour to be followed

**When enlarged retroperitoneal lymph nodes are < 2 cm and with normal markers, treatment should not be initiated unless metastatic disease is unequivocal based on biopsy, increasing nodal size/number, or subsequent marker rise.*
BEP = cisplatin, etoposide, bleomycin; EP = etoposide, cisplatin.

7.2.2.2 Stage II A/B non-seminoma (NSGCT)

Management of CS II A/B NSGCTs encompasses patients in which retroperitoneal nodal disease is present at diagnosis, or appears with relapse following initial surveillance for stage I disease, or marker negative patients with equivocal radiological findings.

All cases of CS II A/B NSGCT with elevated tumour markers at presentation, as well as those in whom nodal disease evolves with a concomitant increase in the tumour marker AFP or β-hCG, require primary chemotherapy according to the treatment algorithm for patients with metastatic disease and according to IGCCCG risk-group (See section 7.2.3).

In CS IIA NSGCT disease without elevated tumour markers, nerve-sparing RPLND when performed by an experienced surgeon in a specialised centre is the recommended initial treatment [202, 203]. Initial surveillance may be considered, in patients with normal markers and lymph nodes < 2 cm of greatest axial diameter, or non-nodular shape with early re-evaluation at six weeks. A shrinking lesion may be observed further. If the lesion progresses further or fails to adequately resolve it should be regarded as CS II and be managed with chemotherapy or primary RPLND based on marker status as outlined in Figure 3.

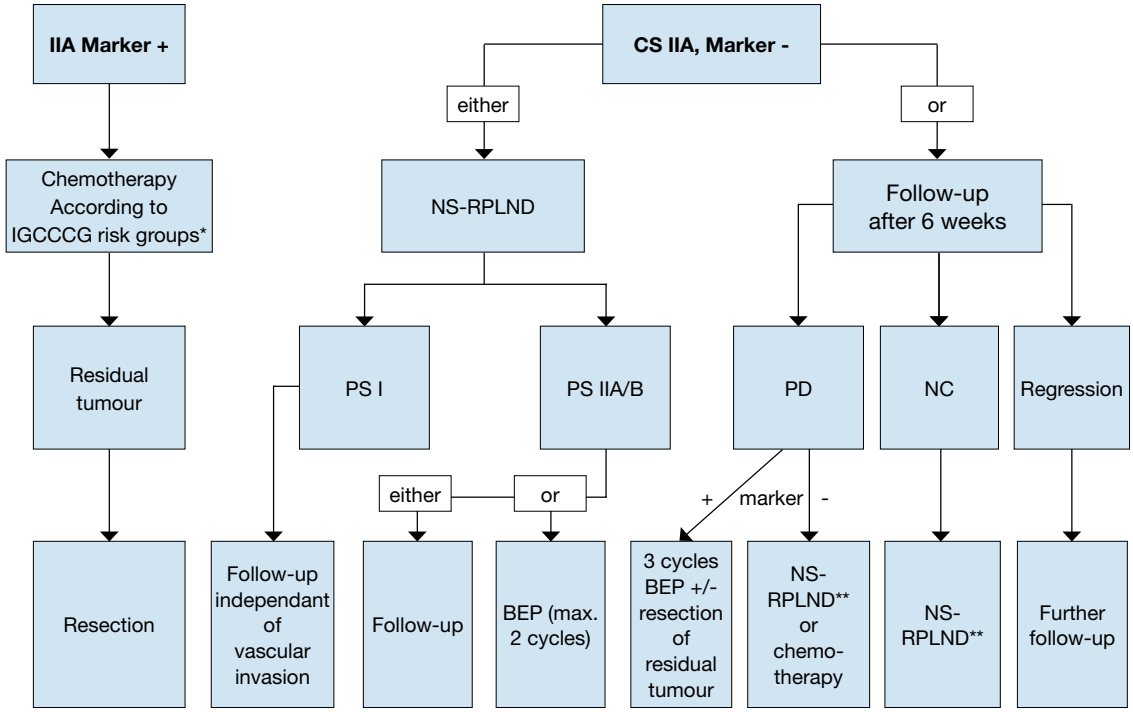
Patients down-staged to PS I require no further treatment even with LVI in the primary tumour site. With PS II disease RPLND alone may be curative. A recent study from Indiana found that 81% of patients with confirmed PS II disease were cured with RPLND alone without additional adjuvant chemotherapy [204]. A further retrospective report on selected patients with stage II relapse after surveillance for stage I NSGCT confirmed a long-lasting remission in 73% of cases following RPLND alone [156]. Relapse, usually outside the retroperitoneum, occurs in 30% of patients with PS II treated with RPLND alone, requiring systemic treatment according to risk-group.

However, adjuvant chemotherapy to reduce the risk of relapse in PS II may be discussed with the patient. Key issues include the risk of overtreatment in about 70% of cases, the need of adequate follow-up to monitor the usually predictable pattern of relapse with minimal but not absent risk of late relapses, the higher relative risk of more intensive therapy in case of relapse, and the possibility of considering quality of surgery and extent of disease (positive lymph node-ratio) as a predictive factor to orient decision. When the choice is for adjuvant chemotherapy, standard treatment is BEP for a maximum of two cycles, but a recent single-centre study of 150 patients undergoing two cycles EP following RPLND and PS II disease reported excellent outcomes with a ten-year relapse-free survival of 98% [205].

Primary RPLND for CS IIA/B disease with elevated markers is not recommended outside a specific study in a referral centre [202, 203].

When a marker negative stage II A/B relapse is diagnosed two or more years after initial diagnosis, a CT- or US-guided biopsy should be advised to confirm the diagnosis of GCT relapse before initiating treatment. A RPLND may be an alternative option and should be performed if biopsy is not feasible or does not provide confirmation of active disease. There is insufficient published data on PET scans in this situation to provide recommendations.

Figure 3: Treatment options in patients with non-seminoma clinical stage IIA



** Most of the patients will be good prognostic group (BEP x3 or PE x4).*
*** In case of PS II A/B patient can be followed-up or receive adjuvant chemotherapy (maximum of 2 cycles).*
BEP = cisplatin, etoposide, bleomycin; NS = nerve-sparing; RPLND = retroperitoneal lymph node dissection; PS = pathological stage; PD = progressive disease; NC = no change.

*7.2.3 **Metastatic disease (stage II C and III)***

7.2.3.1 Primary chemotherapy

7.2.3.1.1 Good-prognosis risk group - seminomatous germ cell tumour

For metastatic seminoma, studies available suggest that a cisplatin-based regimen should be preferred to carboplatin chemotherapy [206].

As data from the GETUG S99 trial indicates that EP x 4 results in cure in almost all cases of good-prognosis SGCTs [207], this regime can also be used; therefore, standard treatment in good-prognosis seminoma should be, BEP x 3 or EP x 4. In the case of contraindications to bleomycin, EP x 4 should be given [208].

Post-chemotherapy masses should be managed as described in Section 7.5.2.

7.2.3.1.2 Intermediate-prognosis risk group - seminomatous germ cell tumour

For patients with intermediate-risk seminoma, BEP x 4 or etoposide, cisplatin, ifosfamide (VIP) when contraindications to bleomycin, are the recommended options, although no RCT has focused specifically on this rare group of patients (see Table 4.3).

7.2.3.1.3 Good-prognosis risk group - non-seminomatous germ cell tumour

For non-seminoma, the primary treatment of choice for metastatic disease in patients with good-prognosis disease, according to the IGCCCG risk classification (Table 4.3.), is BEP x 3 (Table 7.1) [61]. This regimen is superior to cisplatin, vinblastine, and bleomycin (PVB) in patients with advanced disease [208].

The available randomised controlled data support the equivalence of three or four cycles of BEP on a three- or five-day regime for projected two-years PFS. However, the group of patients on the three-days regime experienced increased GI toxicity at three months and increased two-years risk of tinnitus (see section 8.2.6). The difference in toxicity between the three- and five-day regimes reached clinical relevance when BEP x 4 was given [209, 210]. Based on these data the BEP x 3 and a five-day regimen is strongly recommended in the good-prognosis risk group.

Table 7.1: Cisplatin, etoposide, bleomycin (BEP) regimen (interval 21 days)

Drug	Dosage	Duration of cycles
Cisplatin	20 mg/m^2	Days 1-5*
Etoposide	100 mg/m^2	Days 1-5
Bleomycin	30 mg	Days 1, 8, 15

**Plus, hydration.*

Patients with a clear contraindication to bleomycin may receive EP x 4 [209]. In all other cases omission of bleomycin is not recommended.

Two RCTs support the superiority of 3 x BEP over other regimes or schedule intensities [195, 211]. Additionally, a RCT has suggested that when EP is used the mortality rate is twice that as when BEP is used, although the difference did not reach statistical significance [195]. Furthermore, the incidence of residual active cancer in the post-chemotherapy RPLND group was significantly higher in patients who received EP x 4 compared to BEP x 3 (32% vs. 8%, $p < 0.0.01$) [212]. The risk of requiring post-RPLND adjuvant chemotherapy could be higher after EP x 4 which could thereby offset the anticipated advantage of reduced toxicity.

Therapy should be given without reduction of the doses at 21-day intervals. Cytopenias on day fifteen of BEP are common; however, Bleomycin on day fifteen should be given irrespective of neutropenia or thrombocytopenia. Delaying a chemotherapy cycle is justified only in the presence of severe granulocytopenia < 500/mm^3 or thrombocytopenia < 50,000/IU. Mild neutropenia without fever alone is not a reason to delay the next cycle. As Granulocyte colony-stimulating factor (GCS-F) lowers the risk of neutropenic sepsis, one may consider up-front administration. Granulocyte colony-stimulating factor must be given if infectious complications have occurred during or after chemotherapy, or when a treatment interval is delayed due to myelotoxicity [213].

7.2.3.1.4 Intermediate-prognosis risk group - non-seminomatous germ cell tumour

With this group the available data support BEP x 4 as standard treatment [214].

7.2.3.1.5 Poor-prognosis risk group - non-seminomatous germ cell tumour

For patients with a poor-prognosis non-seminoma as defined by the IGCCCG, one standard treatment consists of BEP x 4. Four cycles of cisplatin, etoposide and ifosfamide (PEI) has similar efficacy, but is more myelotoxic [215]. Several RCTs have shown no advantage in OS for upfront high-dose chemotherapy (HDCT) in the overall poor-prognosis patient group [216, 217].

Patients with a slow tumour marker decline after the first or second cycle represent a prognostically inferior subgroup [217, 218]. There are several ways to calculate slow tumour marker decline with an example available at: https://www.gustaveroussy.fr/calculation-tumor/NSGCT.html.

A trial in poor prognosis NSGCT demonstrated that intensifying treatment with dose-dense chemotherapy improves PFS in patients with an early unfavourable tumour marker decline [219]. The trial was not powered

to estimate overall survival. Based on the results from this trial, patients with an unfavourable tumour marker decline after BEP x 1 can be switched to a more intensive (dose-dense) chemotherapy regimen [219]. Further prospective trials/registries are planned to validate this approach. Additional patient groups with an unfavourable prognosis on standard treatment are mediastinal primary non-seminoma and patients with brain metastases at initial diagnosis [220, 221]. These may also be candidates for upfront intensified treatment, preferably in a prospective study.

As a matched-pair analysis comparing high-dose to conventional treatment resulted in a better survival rate [222], poor-prognosis patients should still be treated in ongoing prospective trials or registries, whenever possible. Patients meeting poor-prognosis criteria should be transferred to a specialist centre, as better outcomes are reported for intermediate and poor-prognosis patients treated within a clinical trial at high-volume centres [129, 223]. There are no general recommendations for treatment modifications for patients with poor performance status (Karnofsky < 50%) or extended liver infiltration (> 50%), although two small reports indicate that an initial cycle of dose-reduced therapy may reduce acute mortality without compromising long-term outcome. The number of subsequent cycles of full-dose therapy should, however, not be reduced after an initial low-dose induction cycle [223, 224].

Patients with extended pulmonary infiltration are at risk for acute respiratory distress syndrome (ARDS). They should receive only two to three days of EP, followed by standard chemotherapy when the risk of ARDS has passed (typically after ten days). Management of patients with advanced disease in high-volume centres is associated with improved survival and is consequently recommended [225].

Table 7.2: Level of evidence for prognostic group and treatment

Prognostic group IGCCCG	Treatment	LE
Good (SGCT and NSGCT)	BEP x 3 or PE x 4	1b
Intermediate (SGCT and NSGCT)	BEP x 4 or PEI x 4	1b
Poor (NSGCT)	BEP x 4 or PEI x 4 if favorable marker decline	1b
	Dose escalation in selected cases with slow marker decline	1b

7.2.3.1.6 Prevention of thromboembolism events during chemotherapy

Thromboembolic events (TEE) occur more frequently in patients with GCT receiving chemotherapy than in young males under chemotherapy for other cancers [226]. In Denmark, comparison of TEE incidence between 5,185 GCT patients and 51,850 men without GCT revealed that GCT patients undergoing BEP chemotherapy had significantly more TEE within the first year: with hazard ratios (HRs) of 6.3, 6.0, and 24.7 for myocardial infarction, cerebrovascular accident, and venous thromboembolism, respectively [227]. Indwelling venous access devices (VADs) have been identified as TEE risk factors [228].

Recent RCTs have assessed the risks and benefits of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy and report a relative risk reduction of 30-60% in venous thromboembolic events (VTE) but a doubling of bleeding risk [229-232]. Based on these results, the most recent ASCO Clinical Practice Guideline Update recommends thromboprophylaxis with apixaban, rivaroxaban, or low molecular weight heparin (LMWH) to cancer patients with a high risk of VTE and low risk of bleeding [233]. Metastatic germ cell tumour (mGCT) patients were under-represented in all trials and; thus, it is not clear whether this recommendation applies to this group although retrospective data suggests a similar efficacy of VTE prophylaxis [234].

Several retrospective cohort studies published mGCT specific VTE and bleeding risks as well as potential VTE risk factors. In the largest multi-centre cohort study, men with mGCT showed a cumulative VTE incidence of 11% and < 1% were fatal [235]. Nearly all VTEs occurred shortly prior to or during the first 90 days of commencing chemotherapy [235]. Bleeding was observed in 0.5% (95% CI: 0.02–1%) of men not on thromboprophylaxis, 2.5% (95% CI: 0.3–8.8%) of men on thromboprophylaxis and 3.6% (95% CI: 1.2–8.3%) of patients fully anticoagulated because of VTE [235]. A cumulative VTE incidence of 5% during or after chemotherapy occurred in men without any risk factors for VTE. This would translate to a number needed to treat of 32-55 depending on the assumed efficacy of thromboprophylaxis [228]. If thromboprophylaxis resulted in a similar VTE risk reduction and bleeding risk increase observed in other cancers [229-232], VTE may decrease by a relative risk of 30-60%. This would translate to an absolute risk reduction from 5-10% to 2-5% with the absolute risk of bleeding increasing from <1% to approximately 2-3% [228].

Critics of thromboprophylaxis in mGCT argue that the interobserver reliability of detecting incidental asymptomatic VTEs on staging scans is poor and some asymptomatic VTEs may only represent artifact. Nevertheless only <1% mGCT have asymptomatic VTEs detected on staging scans [228]. Furthermore, incidental VTEs may not truly be asymptomatic as affected patients may have mild symptoms such as cough and fatigue which may be misinterpreted because of the underlying cancer or its associated treatment.

Advocates of thromboprophylaxis contend that reduction of VTE risk may improve outcomes as VTE can be fatal directly or indirectly in <1% of cases. An immediate initial consequence of VTE is the need for therapeutic anticoagulation which is associated with a higher risk of clinically significant bleeding [228, 236] including critical areas particularly intracerebral and complicate post chemotherapy surgery. Venous thromboembolic events may also result in long term complications including post-thrombotic syndromes leading to venous leg ulceration and chronic pain. Similarly, pulmonary embolism can impair right ventricular function and pulmonary arterial pressure that does not resolve in 10-30% of patients, with up to 4% ultimately developing chronic symptomatic pulmonary hypertension [237]. These complications all reduce QoL and increase lifetime healthcare costs.

Based on disease specific VTE risk assessments in numerous retrospective cohort studies and the long life-expectancy of mGCT patients, the European Association of Urology Testis Cancer Guideline panel has discussed a recommendation regarding thromboprophylaxis. All members agreed that men with mGCTs undergoing chemotherapy are at high-risk for VTE and low-risk of bleeding. Although several mGCT specific VTE risk factors have been described in the literature [238] only data from retrospective cohorts is available, VTE outcome definitions are heterogeneous and, in most of the studies, only univariable analyses without external validation were performed. Given the apparent high VTE incidence and only non-validated VTE risk factors, the panel preferences were divided between those panel members that favoured thromboprophylaxis in all men and those panel members that restricted thromboprophylaxis to men with certain risk factors. For the final guideline recommendation, the panel agreed that based on the current literature only a generic statement about the use of thromboprophylaxis should be given until stronger evidence is available. Therefore, RCTs or well conducted prospective cohort studies with an adequate sample size allowing adjusting for potential confounders and numerous risk factors are needed to clarify the indication for thromboprophylaxis.

However, no randomised trials are underway to answer those questions and the only two retrospective studies analysed the risk benefits of thromboprophylaxis reported contradictory results [234, 239]. Both studies only had a limited number of men with VTE limiting the ability to account for known confounders which limits the conclusion from both studies.

A generic statement in the TC Guideline should remind clinicians about the high VTE incidence and to prescribe thromboprophylaxis after balancing the risk and benefits. Additionally, the majority of the panel agreed that a central venous-access device should be avoided whenever possible as this represents the only modifiable risk factor which remained significantly associated with VTE in a multivariable risk-prediction model [228].

Thromboprophylaxis includes either LMWH or oral thromboprophylaxis (apixaban 2.5 mg bid or rivaroxaban 10 mg qd) starting before chemotherapy and continued for at least 90 days. Thromboprophylaxis should only be prescribed if no drug interactions or significant risk factors for bleeding are present. Although GCT patients specific risk factors for bleeding are ill-defined the personal experience of panel members and case reports suggest that men with organ infiltration, cerebral metastases and/or significantly elevated β-hCG levels suggestive of choriocarcinoma are at a higher risk of bleeding.

Summary of evidence	**LE**
Thromboembolic events occur more frequently in male patients with GCTs receiving chemotherapy than in young males under chemotherapy for other cancers.	2b
Retrospective studies have identified multiple risk factors for the development of thromboembolic events including increasing stage, size of retroperitoneal lymph nodes at different cut-offs, Khorana score ≥ 3 and indwelling vascular access device (only modifiable risk factor).	2b

Recommendations	**Strength rating**
Balance the individual patients' potential benefits and risks of thromboprophylaxis during first-line chemotherapy in men with metastatic germ cell tumours.	Weak
Avoid use of central venous-access devices during first-line chemotherapy whenever possible.	Weak

7.3 Treatment evaluation and further treatment

*7.3.1 **Treatment evaluation***

Response to treatment should be assessed after the initial induction cycle by repeat imagining and/or re-evaluation of tumour markers. With marker decline and/or radiologically regressing or stable tumour features, the planned chemotherapy, based on prognostic group, should be completed [240, 241]. If markers decline, but metastases progress on imaging, induction therapy must be completed followed by early resection [242].

With initial disease progression following induction (primary cisplatin refractory), patients should be switched to experimental drug trials [243]. Slow marker decline with the initial one to two cycles of chemotherapy warrants consideration for dose intensification (see section 7.2.3.1.5).

Following completion of treatment, cases with a low-level β-hCG plateau should be observed to determine whether complete normalisation subsequently occurs. In patients with a low plateau serum AFP level after chemotherapy, removal of residual masses should be undertaken, with subsequent AFP monitoring. Salvage chemotherapy is only indicated for documented marker progression [244, 245].

*7.3.2 **Residual tumour resection***

7.3.2.1 Seminoma

A residual mass of seminoma should be monitored with imaging and tumour markers and not primarily resected, irrespective of size [246-249]. Those with AFP elevation should be regarded as mixed GCTs, be managed as NSGCTs and considered for surgical resection. False-positive AFP elevation (e.g., due to liver toxicity after chemotherapy) has to be excluded.

Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with residual masses after treatment of seminoma. False positive results are less frequent when scans are scheduled more than two months after chemotherapy. In patients with residual masses > 3 cm, FDG-PET should be performed in order to provide more information on disease viability. In patients with residual masses < 3 cm, the use of FDG-PET may be useful, but it is optional [55, 56].

When a post-chemotherapy mass remains positive at reclassification with FDG-PET with no volume increase, repeat FDG-PET should be performed six weeks later. A recent publication shows a low PPV for vital tumours in residual lesions (generally > 3 cm) after chemotherapy in metastatic seminoma (11% to 38% depending on sub-group). Therefore, caution is recommended with FDG-PET as a single parameter to drive clinical decisions in a persistent mass [57]. In patients with progressive disease on radiological criteria (i.e., a growing mass which enhances with CECT or is FDG-PET avid), salvage therapy is indicated (usually chemotherapy or radiotherapy) [250-252]. Surgery may be an option in patients with a residual nodular mass and contraindications to further chemotherapy or irradiation.

Patients with persistently high and/or progressing β-hCG elevation after first-line chemotherapy should proceed to salvage chemotherapy. Progressing patients without β-hCG progression should undergo histological verification (e.g., by percutaneous or surgical biopsy) before salvage chemotherapy is given. When RPLND is indicated, this should be performed in referral centres, as residual seminoma masses may be extremely difficult to remove due to intense fibrosis [251]. Ejaculation may be preserved in some of these cases [253].

7.3.2.2 Non-seminoma

Following first-line BEP chemotherapy, only 6-10% of residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only [254]. Fluorodeoxyglucose-positron emission tomography is not indicated to re-stage patients following chemotherapy [50, 52, 53]. With complete radiological remission, RPLND is not indicated [255, 256].

Usual timing for restaging is three to four weeks after the beginning of the last cycle. No diagnostic or risk calculator can accurately predict histology of the residual masses. Thus, resection is mandatory in all patients with a residual mass > 1 cm in greatest axial diameter at cross-sectional CECT imaging until novel predictive models are externally validated [257-260]. Surgery when indicated should be performed within six to eight weeks after the last chemotherapy cycle.

There is uncertainty regarding the role of surgery with residual retroperitoneal lesions < 1 cm. It is difficult to distinguish between a true residual node below 10 mm and a complete remission, and many authors consider these situations as equivalent. Residuals containing cancer or teratoma are possible, but the vast majority of patients have fibro-necrotic tissue only [261]. So far, post-chemotherapy RPLND in case of residuals < 10 mm

or complete remission is an option [262], but the alternative option is an observation protocol with recurrence risk of 6-9% depending on the follow-up duration [255, 256]. In the series with the longest follow-up of 15.5 years, twelve (9%) of 141 patients relapsed despite a complete response following primary treatment [256]. Eight of the twelve relapsing patients were cured with subsequent treatment. These cases should be discussed on individual basis taking into account the orientation and expectations of the patient.

Patients after salvage chemotherapy or HDCT in first or subsequent salvage situations harbour vital tumour at a much higher rate [263]. Surgery is therefore indicated in salvage patients even with residual masses < 1 cm [255, 256].

When resection is indicated bilateral nerve-sparing RPLND is the standard option. Ipsilateral template resection avoids contralateral nerve dissection and leads to improved functional results together with favourable clinical results although mapping studies describe the risk of missed contralateral disease [264].

In men with post-chemotherapy residuals with a residual diameter < 5 cm [265], as well as unilateral lymph node metastases on pre- and post-chemotherapy CT scans, left-sided tumours only require para-aortic resection whereas right-side tumours need paracaval and interaortocaval resection down to the iliac arteries [266, 267].

Indications for ipsilateral template resection after first-line chemotherapy represent men with a residual tumour volume < 5 cm and ipsilateral metastatic disease on pre- and post-chemotherapy scans. The mere resection of the residual tumour (so called lumpectomy) should not be performed [256, 260, 261, 263, 265, 267, 268].

Laparoscopic or robotic RPLND may yield comparable outcomes to open procedures in selected cases with low-volume residual disease and when undertaken by very-experienced surgeons. This should only be considered in specialist TC centres with expertise in open RPLND and minimally invasive surgery to ensure appropriate case selection. In this setting, up to 30% of post-Chemotherapy RPLND have been reported via a laparoscopic approach [269-271]. Experience with robot-assisted laparoscopic RPLND remains limited [272] and atypical recurrences have been reported, and occur more often, with this approach [167].

7.3.3 ***Sequencing of surgery in the case of multiple sites***

In general, surgery should commence at the site with the highest volume of residual disease. The histology of the mass diverges in different organ sites [257]. In cases of residual retroperitoneal and lung masses, the presence of fibro-necrotic tissue in the retroperitoneum is associated with a probability as high as 90% that lung masses contain the same histology [273]. Resection of contralateral pulmonary lesions is not mandatory when pathologic examination of the lesions from the initial side show complete necrosis. Discordant histology between lung sites, however, may occur in up to 20% of cases [274, 275].

7.3.3.1 Quality and intensity of surgery

Post-chemotherapy surgery is always demanding. Whilst most post-chemotherapy RPLNDs do not require resection of major vessels or organs, a proportion of patients may require an intervention in which organs affected by the disease are removed in order to achieve radical resection (e.g., kidney, psoas muscle or gross vessels), and may potentially also require *ad hoc* reconstructive surgery (e.g., vascular interventions such as vena cava or aortic prostheses). Patients undergoing adjunctive complex surgery benefit from disease control but have a greater risk of complications [276, 277]. In patients with intermediate- or poor-risk and residual disease > 5 cm, the probability of vascular procedures is as high as 20% [278]. This “maximal” surgery must therefore be referred to specialised centres capable of interdisciplinary surgery (hepatic resections, vessel replacement, spinal neurosurgery, thoracic surgery). Even with centralisation of treatment, the median number of RPLNDs performed per surgeon/year in the U.K. is six [279]. Nevertheless, patients treated within such centres benefit from a significant reduction in peri-operative mortality from 6-0.8% [280]. In addition, specialised urologic surgeons are capable of reducing the local recurrence rate from 16-3% with a higher rate of complete resections [281].

7.3.3.2 Salvage and desperation surgery

Surgery of resectable disease after salvage treatment remains a potentially curative option in patients with any residual mass following salvage chemotherapy. Survival after surgery and first salvage chemotherapy improved by 70% at ten years, following taxane-containing regimens [282]. Also, even with extensive salvage chemotherapy, surgery remains a fundamental tool to achieve durable complete remissions in up to 20% of patients [283, 284].

Desperation surgery refers to resection of non-responsive or progressive (e.g., rising markers) disease following salvage chemotherapy. When the disease is resectable, a significant proportion of these patients can be rendered disease-free in the long term [285].

7.3.3.3 Consolidation chemotherapy after secondary surgery

After resection of necrosis or post-pubertal teratoma, no further treatment is required. In cases of incomplete resection of viable cancer, two adjuvant cycles of conventionally dosed cisplatin-based chemotherapy may be given in certain subgroups (e.g., poor-prognosis patients) [268]. However, caution is required with cumulative doses of bleomycin. After complete resection of 'vital' tumour < 10% of the total volume, particularly in patients who initially had a good-prognosis based on IGCCCG criteria, the relapse rate is very low and adjuvant chemotherapy is not beneficial in preventing further relapse [286]. The prognosis is worse if malignant disease is present in masses resected after second- and third-line chemotherapy. In this latter situation, post-operative chemotherapy is not indicated [287].

*7.3.4 **Systemic salvage treatment for relapse or refractory disease***

Cisplatin-based combination salvage chemotherapy will result in long-term remissions in approximately 50% of patients who relapse after first-line chemotherapy. These results are highly dependent on several prognostic factors [288]. The regimens of choice are four cycles of a three-agent regimen including cisplatin and ifosfamide plus a third drug: etoposide (PEI/VIP), paclitaxel (TIP), or potentially gemcitabine (GIP) (Table 7.3) [289, 290]. No RCT has compared these regimens. Due to their potential risk of lethal haematological toxicity, these regimens should be used with G-CSF support and by well-trained oncologists.

The only available RCT comparing standard-dose and HDCT plus transplantation in the salvage setting showed no benefit in OS in patients treated with three cycles of vinblastine, ifosfamide, and cisplatin (VeIP) plus one cycle of consolidation HDCT, compared with VeIP x 4 [291]. For methodological reasons, this trial design can no longer be considered state of the art.

Table 7.3: Standard PEI/VIP, TIP and GIP salvage chemotherapy (interval 21 days)

Regimen	Chemotherapy agents	Dosage	Duration of cycles
PEI/VIP	Cisplatin*	20 mg/m^2	Days 1-5
	Etoposide	75-100 mg/m^2	Days 1-5
	Ifosfamide†	1.2 g/m^2	Days 1-5
TIP	Paclitaxel	250 mg/m^2 [xx]	24 hour continuous infusion day 1
	Ifosfamide†	1.5 g/ m^2	Days 2-5
	Cisplatin*	25 mg/m^2	Days 2-5
	Alternative schedule		
	Paclitaxel	175 mg/m^2	Day 1, 3 hour infusion
	Ifosfamide†	1.2 g/m^2	Days 1-5
	Cisplatin*	20 mg/m^2	Days 1-5
GIP	Gemcitabine	1000 mg/m^2	Day 1 + 5
	Ifosfamide	1200 mg/m^2	Days 1-5
	Cisplatin	20 mg/m^2	Days 1-5

** Plus, hydration.*

† Plus, mesna protection.

[xx] An MRC schedule uses paclitaxel at 175 mg/m^2 in a 3 hour infusion [290].

A retrospective analysis by the International Prognostic Factors Study Group (IPFSG) evaluated the risk of relapse in patients in whom this occurred after at least three cisplatin-based cycles and subsequent cisplatin-based conventional-dose or carboplatin-based high-dose salvage chemotherapy [189]. Seven variables - histology, primary tumour location, response, progression-free interval after first-line treatment and level of AFP, hCG and the presence of liver, bone or brain metastasis at salvage treatment were identified as independent prognostic variables of relapse after initial cisplatinum-based chemotherapy [189]. Using these factors, five risk-groups: very low-risk = -1 points; low-risk = 0 points; intermediate-risk = 1-2 points; high-risk = 3-4 points; and very high-risk > 5 points; were identified with significant differences in PFS and OS. Table 7.4 illustrates these five risk groups and the corresponding two-year PFS and three-year OS rates [189]. Several recent trials have validated this scoring system [292-295]. As in first-line therapy, the prognostic impact of tumour marker decline applies in the salvage setting [296]. While progression to induction chemotherapy was negative for OS, prior use of paclitaxel was not significantly associated with a negative outcome [297].

A secondary analysis of the IPFSG cohort (n = 1,600 patients) showed an improvement of about 10-15% in OS in all prognostic subgroups when treated with high-dose salvage therapy compared to standard dose therapy. To prospectively confirm this finding, an RCT of high-dose vs. conventional dose chemotherapy in patients with first-line relapse is underway (Tiger trial). When HDCT is used as a salvage treatment, sequential treatment cycles of high-dose carboplatin and etoposide (HD-CE) should be preferred to a single high-dose regimen as the former is associated with less toxicity-related deaths [292]. A recent systematic review confirmed the superiority of using at least two high-dose cycles in the salvage setting over a single high-dose cycle [298]. It is clearly of the utmost importance that these rare patients with relapse are treated within clinical trials and at specialised centres.

Table 7.4: The International Prognostic Factors Study Group Score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [189]

Points	**-1**	**0**	**1**	**2**	**3**
Variable					
Histology	Seminoma	Non-seminoma			
Primary site		Gonadal	Retroperitoneal		Mediastinal
Response		CR/PRm-	PRm+/SD	PD	
PFI		> 3 months	≤ 3 months		
AFP salvage		Normal	< 1000	1000	
hCG salvage		< 1000	1000		
LBB		No	Yes		

AFP = alpha-fetoprotein; CR = complete remission; PRm- = partial remission, negative markers; PRm+ = partial remission, positive markers; hCG = human chorionic gonadotrophin; LBB = liver, bone, brain metastases; PD = progressive disease; PFI = progression-free interval; SD = stable disease.

Table 7.5: PFS and OS estimates for all patients according to IGCCCG prognostic score for seminoma and non-seminoma that relapse after cisplatin-based first-line chemotherapy [190]

Score (n = 1,435)	**N**	**%**	**HR**	**2-years PFS (%)**	**3-year OS (%)**
Very Low	76	5.30	1	75.1	77.0
Low	257	17.9	2.07	52.6	69.0
Intermediate	646	45.0	2.88	42.8	57.3
High	351	24.5	4.81	26.4	31.7
Very High	105	7.3	8.95	11.5	14.7
Missing	159	-	-	-	-

HR = hazard ratio; PFS – progression-free survival; n = number of patients; OS = overall survival.

*7.3.5 **Second relapse***

No RCTs have been reported for patients with second relapse and overall conventional therapy does not appear effective. For patients who have received two series of conventionally dosed therapy (first-line and first-salvage), high-dose chemotherapy with autologous stem cell support should be used [293]. With this the prospect of cure is only 20% to 25%.

Patients relapsing within four to eight weeks after platinum-based therapy, or who are progressing despite platinum-based therapy, as well as those relapsing shortly after high-dose chemotherapy, are considered as cisplatin refractory. Combinations of gemcitabine and oxaliplatin or the triple combination of gemcitabine, oxaliplatin and paclitaxel have resulted in response rates of 25-45% in this setting. Cisplatin re-challenge in association with gemcitabine and paclitaxel may be considered in patients with adequate renal function [299]. For patients with a second relapse not responding to the combination of oxaliplatin and gemcitabine or the triple combination, inclusion in clinical trials is encouraged.

Patients with a good response undergoing subsequent resection of residual tumour lesions may still have a 15-20% chance of long-term cure [283, 300].

Various targeted agents have generally failed in refractory disease, including immune checkpoint inhibitors [292-298, 301]. Trials combining PD1/PDL-1 and CTLA4 inhibitors are ongoing; however, even for those combinations early results are not encouraging.

7.3.5.1 *Late relapse (more than two years after end of first-line treatment)*

Late relapse is defined as recurrence more than two years after completion of successful primary treatment of metastatic TC [54]. According to a pooled analysis, this occurs in 1.4% and 3.2% of seminoma and non-seminoma patients, respectively [302]. Interestingly, in a population-based study all late-relapsing seminoma patients had viable GCT [303]. These can be treated with chemotherapy and radiotherapy.

In contrast, patients with late-relapsing NSGCT should undergo surgical resection when feasible, alone or in combination with chemotherapy. Some patients, including those with rapidly rising β-hCG, may benefit from induction salvage chemotherapy with subsequent reconsideration of surgery for resection of persisting residual masses [202]. In general, however, surgery represents the mainstay of treatment, and it should be performed in most patients when feasible irrespective of the level of their tumour markers in order to completely resect all viable GCT post-pubertal teratoma or TSTC [202, 304]. Survival strongly relates to the histology of the recurrent lesions rather than that of the initial disease. If not completely resectable, biopsies should be obtained for histological evaluation to direct salvage chemotherapy based on the tumour phenotype. Review by an experienced pathologist is critical to avoid misinterpretation of the therapeutic morphological changes that occur with the treatment of GCT [305]. If the patient responds to salvage chemotherapy, secondary surgery should then be undertaken if feasible. With unresectable, but localised refractory disease, stereotactic or conventional radiotherapy may be considered. To avoid excess mortality, late relapses should be treated only at centres experienced in managing such patients [306].

7.3.6 ***Treatment of brain metastases***

Brain metastases occur in the context of initial metastatic disease, systemic relapse and rarely as an isolated site of relapse. Long-term survival of patients presenting with brain metastases at diagnosis is poor (30-50%) and even poorer when a site of recurrent disease (five-year survival-rate is 2-5%) [307, 308]. A large international database comprising 523 patients reported 48% three-year OS rates in patients with brain metastases at initial diagnosis and 27% three-year OS rates for patients with brain metastases at relapse [45].

Chemotherapy as initial treatment proved effective in a first-line setting (potentially even as dose-intensified therapy upfront) with data also supporting the use of multimodal treatment particularly in relapsed disease [45]. Consolidation RT, even with total response after chemotherapy, should therefore be used in patients with brain metastases at relapse, but must be carefully discussed in a first-line setting [309]. Surgery may be considered in cases with a persistent solitary metastasis, depending on the systemic disease status, histology of the primary tumour and the location of the metastasis.

7.3.6.1 *Guidelines for the treatment of metastatic testicular germ cell tumours*

Summary of evidence	**LE**
In the NSGCT good-prognosis-risk group (IGCCG), BEP x 3 is superior to other chemotherapy regimens. Toxicity is lower when treatment is delivered in five-day regimes rather than three-day regimes.	1b
In NSGCT intermediate-prognosis-risk group (IGCCCG) BEP x 4 is the standard treatment of choice with a five-year survival of 89% in contemporary series.	1b
In pathological stage II NSGCT disease, RPLND performed in specialised centres without adjuvant chemotherapy results in 73-81% of long-lasting remissions.	2b
In patients with a poor-prognosis metastatic NSGCT (defined by IGCCCG), treatment with BEP x 4, results in a five-year PFS of 67%. There is no advantage in OS for high-dose chemotherapy.	1b
Patients with a poor-prognosis metastatic NSGCT and early unfavourable tumour marker decline may benefit from intensification of treatment with dose-dense chemotherapy, with improvement of PFS despite no benefit being observed for OS.	1b
Following first-line BEP chemotherapy, 6-10% of NSGCT residual masses contain active cancer, 50% have post-pubertal teratoma, and 40% comprise of necrotic-fibrotic tissue only. Figures regarding persistence of residual active are slightly lower in post chemotherapy residual masses < 1 cm. Currently there is no accurate prognostication method of histology.	2b
In CS IIA/B seminoma radiotherapy and chemotherapy treatment show similar effectiveness, with a non-significant trend towards greater efficacy of chemotherapy in CS IIB. However, risk of second malignancies and cardiovascular events is higher after radiotherapy.	2a
In metastatic seminoma stage ≥ IIC, primary chemotherapy with BEP, tailored to the IGCCCG risk group, has proven superior to Carboplatin based chemotherapy.	1b
Fluorodeoxyglucose-positron emission tomography has a high NPV in patients with post-chemotherapy seminoma residual masses (> 3 cm) when performed more than two months after chemotherapy.	2b

Recommendations	Strength rating
Treat low-volume non-seminomatous germ cell tumour (NSGCT) stage IIA/B with elevated markers like metastatic good- or intermediate-prognosis risk group IGCCCG with three or four cycles of cisplatin, etoposide, bleomycin (BEP).	Strong
Nerve-sparing retroperitoneal lymph node dissection when performed by an experienced surgeon in a specialised centre is the recommended initial treatment in clinical stage (CS) IIA NSGCT disease without elevated tumour markers.	Weak
Repeat staging after six weeks before making a final decision on further management should be considered in patients with small volume (CS IIA < 2 cm) marker-negative NSGCT.	Weak
Treat metastatic NSGCT (stage ≥ IIC) with an intermediate prognosis with four cycles of standard BEP	Strong
In metastatic NSGCT with a poor-prognosis, treat with one cycle of BEP, (or cisplatin, etoposide and ifosfamide [PEI], in cases with pulmonary dysfunction), followed by tumour marker assessment after three weeks. Continue the same schedule up to a total of four cycles with favourable marker decline. With unfavourable decline, initiate chemotherapy intensification.	Weak
Perform surgical resection of visible (> 1 cm) residual masses after chemotherapy for NSGCT when serum levels of tumour markers are normal or normalising.	Strong
Initially offer cisplatin-based chemotherapy according to IGCCCG prognosis groups, or alternatively radiotherapy to seminoma patients with stage II A/B and, inform the patient of potential long-term side effects of both treatment options.	Weak
Treat seminoma stage IIC and higher, with primary chemotherapy according to IGCCCG classification (BEP x 3 in good-prognosis and BEP x 4 in intermediate prognosis).	Strong

8. FOLLOW-UP AFTER CURATIVE THERAPY

8.1 Minimal recommendations for follow-up

Based on different risks of relapse depending on diagnosis and initial treatment, three major follow-up groups can be defined:

1. patients with seminoma stage I;
2. patients with non-seminoma stage I on active surveillance;
3. all patients having received either adjuvant treatment or curative chemotherapy for “good”- and intermediate-prognosis metastatic disease (according to the IGCCCG) achieving a complete remission with, or without, surgery (for seminoma this includes residual lesions < 3 cm, or residual lesions > 3 cm that are PET-negative).

It is important to note that patients not achieving a complete remission or presenting with poor-prognosis disease should be followed up individually by specialised centres. Tables 8.1-8.3 show the minimal recommendations for follow-up of the three different groups based on recommendations developed at a European Society for Medical Oncology (ESMO) consensus conference [310].

Both CT and MRI can be used to evaluate the retroperitoneum, pelvis and inguinal regions for sites of metastatic disease from TC [311]. Magnetic resonance imaging benefits from an absence of ionising radiation but is more time consuming and less readily available than CT [312]. Given the frequency of follow-up, over a number of years some studies have estimated a risk of up to 1 in 300 of second malignancy related to CT imaging follow-up alone [51], although more recent dose saving protocols and limitations on field of view will have mitigated this somewhat. Nevertheless, this risk could be excluded by the use of MRI for follow-up.

Both CT and MRI rely predominantly on size cut-offs for evaluation given the excellent spatial resolution of both modalities, with morphological assessment for features such as necrosis and irregular shape an adjunct. Sensitivity and specificity vary according to the size cut-off used [311]. However, studies have shown comparable excellent results between CT and MRI with up to 98% sensitivity on MRI for the detection of retroperitoneal nodal metastases in TGCT [313]. It has, however, been demonstrated that reader experience is important when interpreting images [314]. In the setting of TGCT, one study demonstrated decreased sensitivity for detection of retroperitoneal nodal disease on MRI when reported by a trainee radiologist with sensitivity of detection of 80% [51]. However, experienced radiologists in the same study again achieved sensitivity for detection of nodal disease of 97% with good interobserver agreement. It was therefore suggested that if MRI is

to be used instead of CT for follow-up this be done in centres/units with oncological radiologists who routinely report CT and MRI in patients with TGCT rather than general radiologists who may only occasionally see such imaging. Consequently, MRI of the abdomen can be used as an alternative to CECT in experienced centres [315].

Regarding the use of US examination of the contralateral testis, the majority of the consensus meeting participants did not support repeat US investigation, either with negative biopsy or if no contralateral biopsy has been performed [310].

A very late relapse (VLR) after five years is a rare event occurring in approximately 0.5% of patients based on a population-based analysis [303]. The aim of follow-up beyond five years therefore shifts to detection of late side effects of treatment, and imaging tests are not routinely recommended.

Most patients with VLR are diagnosed due to symptoms, although up to 50% elevated tumour markers are present in both seminoma and NSGCTs [303, 316]. Patient education regarding relapse symptoms and clinician awareness are important elements of survivorship management. Early use of imaging and tumour markers with suspicion of relapse is encouraged.

Table 8.1: Recommended minimal follow-up for seminoma clinical stage I on active surveillance or after adjuvant treatment (carboplatin or radiotherapy)

Modality	Year 1	Year 2	Year 3	Years 4 & 5	After 5 years
Tumour markers ± doctor visit	2 times	2 times	2 times	Once	Further management according to survivorship care plan
Chest X-ray	-	-	-	-	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	2 times	2 times	Once at 36 months	Once at 60 months	

Table 8.2: Recommended minimal follow-up for non-seminoma clinical stage I on active surveillance

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times*	4 times	2 times	1-2 times	Further management according to survivorship care plan
Chest X-ray	2 times	2 times	Once, in case of LVI+	At 60 months if LVI+	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging	2 times	At 24 months**	Once at 36 months***	Once at 60 months***	

* *In case of high-risk (LVI+) a minority of the consensus group members recommended six times.*

** *In case of high-risk (LVI+) a majority of the consensus group members recommended an additional CT at eighteen months.*

*** *Recommended by 50% of the consensus group members.*

LVI+ = Lymphovascular invasion present

Table 8.3: Recommended minimal follow-up after adjuvant treatment or complete remission for advanced disease (excluded: poor-prognosis and no remission)

Modality	Year 1	Year 2	Year 3	Year 4 & 5	After 5 years
Tumour markers ± doctor visit	4 times	4 times	2 times	2 times	Further management according to survivorship care plan**
Chest X-ray	1-2 times	Once	Once	Once	
Abdominopelvic computed tomography (CT)/magnetic resonance imaging (MRI)	1-2 times	At 24 months	Once at 36 months	Once at 60 months	
Thorax CT	1-2 times*	At 24 months*	Once at 60 months*	Once at 60 months*	

* *In conjunction with abdominopelvic CT/MRI in case of pulmonary metastases at diagnosis.*

** *In case of teratoma in resected residual disease: the patient should remain with the uro-oncologist.*

8.2 Quality of life and long-term toxicities after cure of testicular cancer

The vast majority of patients will be cured with five-year relative survival rates of approximately 95% in Western Europe. Testicular cancer patients are usually between 18 and 40 years of age at diagnosis and life expectancy after cure extends over several decades [317]. Patients should be informed before treatment of common long-term toxicities, which are avoided or minimised by adherence to international guidelines.

Treatment of stage I TC is controversial, with some experts advocating surveillance for all, thereby avoiding unnecessary adjuvant chemotherapy [159], whereas others highlight the importance of patient autonomy and consider the prospect of avoiding salvage treatment with long-term toxicities appealing [318]. Unfortunately, it is not known which treatment spares most patients from long-term toxicities, which so far seem to be absent or mild after adjuvant chemotherapy. This observation is confirmed by the absence of excess mortality or late toxicities between stage I non-seminoma patients randomised to either primary RPLND or one cycle of adjuvant BEP [319].

During follow-up, patients should be screened and treated for known risk factors such as hypertension, hyperlipidaemia, and testosterone deficiency. Adverse health outcomes (AHOs) are more commonly found in TC patients who received chemotherapy than those cured by surgery alone. Further, modifiable risk factors do contribute to AHOs like hypertension and noise exposure to hearing impairment or smoking to Raynaud phenomenon [320]. Therefore, a healthy lifestyle should be promoted during the follow-up consultations. Adverse health outcomes are associated with unemployment, which is found clearly increased in TCSs as compared to a male normative population [321]. When follow-up by the TC clinician is terminated, a written cancer survivorship plan addressing late toxic effects, lifestyle recommendations, recurrence risk, and cancer-specific follow-up may be helpful [54, 322].

8.2.1 Second malignant neoplasms (SMN)

Metachronous contralateral TC represents a particular SMN as it consists of a GCT. Further, cisplatin-based chemotherapy approximately reduces the risk of a subsequent contralateral TC as compared to surgery only [323, 324]. Second malignant neoplasms of different histologic origin usually occur after the first ten years and are considered to be induced by chemo- and/or radiotherapy [322]. Testicular cancer is commonly diagnosed in adolescents and young adults (AYA), which have a higher absolute risk of developing a subsequent primary neoplasm than survivors of childhood or adult cancer [325]. In a comprehensive study on second cancers in AYA cancer survivors (aged 15-39 years at AYA cancer diagnosis), 24,309 TC survivors with 1,435 second cancers were registered as opposed to 808 expected second cancers, yielding a standardised incidence ratio of 1.8. The second cancer incidence increased with time resulting in remarkably high and accelerating 35-year cumulative incidence rate of 20% (95% CI: 18·9–21·5) [325].

The risk for solid SMN increases with younger age at radio- or chemotherapy [322]. Radiotherapy-related SMN are primarily localised within, or close to, the radiotherapy field (colon, stomach, pancreas, bladder, and the urinary tract) [322]. A remarkably clear radiation-dose relationship to gastric- and pancreatic cancer has been demonstrated [326].

Modern cisplatin-based chemotherapy has been found to be associated with a 40% increased risk of a solid SMN [327]. A relationship between cumulative dose of cisplatin and second SMN, especially in the GI tract, has been noted [328]. As few studies have observation times beyond 25 years, the cumulative incidence of SMN may be underestimated. An increase from 6.5% after 25 years to 20% after 35 years has been

reported [325]. Second malignant neoplasms were identified in 9.4% of Swedish TC survivors, with half these cancers considered uncommon in men in their 40s [329]. Survival was 40% in TC survivors with a SMN as opposed to 80% in those without [329].

The European Society for Blood and Marrow Transplantation (EBMT) reported SMN in 59 of the 5,295 TC patients registered after receiving HDCT within a median follow-up of 3.8 years. Of them, 39% developed a hematologic SMN and 58% a solid SMN. Twenty-year cumulative incidence of solid and hematologic SMN was 4.2% and 1.4% respectively, with median OS shorter after diagnosis of hematologic vs. solid SMN (8.6 vs. 34.4 months). Age ≥ 40 years at the time of HDCT was significantly associated with hematologic, but not with solid SMNs [330]. Among 24,900 US TCSs, one out of six (16.9%) developed a solid SMN after 30 years of observation time [331].

*8.2.2 **Leukaemia***

In a series of 40,576 TC survivors, the observed ratio for developing leukaemia, mostly acute myeloid (AML) and lymphoblastic leukaemia was 2.6 [332]. Among 24,900 US TCSs, the risk of developing leukaemia, mostly AML, after chemotherapy was 2.7 fold increased [331]. The risk of AML seems to be related to both the dose of cisplatin and etoposide. Doses of etoposide exceeding 2 g/m^2 have been shown to increase the subsequent risk of AML [333]. The majority of TC patients receive much lower doses of etoposide than this so that the absolute risk of AML after three to four courses of BEP is very low. In patients requiring HDCT with cumulative etoposide doses exceeding this threshold, fewer than 1.5% have been reported to develop AML. There is a cumulative dose disease risk relationship with cisplatin and AML. Chemotherapy-induced leukaemia is usually diagnosed within the first ten years after treatment for TC and has a poor-prognosis [334].

*8.2.3 **Infections***

Chemotherapy-treated TC survivors (TCSs) have a higher risk of dying from infections than the general population (standard mortality ratio 2.48, 95%; CI: 1.70-3.5) [335]. This is possibly due to long-term bone marrow suppression, as well as complications of subsequent salvage treatment (which was not reliably registered). Alternatively, extensive or subsequent surgical treatment may be contributory. Furthermore, asymptomatic pulmonary fibrosis by mediastinal radiotherapy and/or bleomycin may render TCSs vulnerable to respiratory infections long after treatment.

*8.2.4 **Pulmonary complications***

Chemotherapy exposed TCSs have a nearly three-fold increased risk of dying of pulmonary diseases than the normal population [335]. Bleomycin-induced lung toxicity may affect 7-21% of patients in the long term, resulting in death in 1-3% [336]. Testicular cancer survivors who received high cumulative cisplatin doses and/or pulmonary surgery, have a poorer pulmonary function than those cured with surgery alone [325]. Intriguingly, long-term pulmonary complications were associated with the cumulative cisplatin doses but not with the dose of bleomycin [337]. The data contrasts with a meta-analysis on chemotherapy for TC including 6,498 patients showing a significant effect of bleomycin administration on all-grade pulmonary toxicity [338]. In a Danish cohort of 565 TC survivors, Lauritsen *et al.*, found pulmonary function recovered with repeated assessments over five years in almost all patients [339]. Pulmonary function was not associated with reduced renal function, age, tobacco-smoking, and cumulative chemotherapy, but rather pulmonary embolism, lung surgery, and poor IGCCCG risk group [339]. In 234 good risk TCSs patients the inclusion of bleomycin did not seem to influence pulmonary morbidity, operative difficulty, or non-pulmonary post-operative complications after post-chemotherapy RPLND [340].

A Canadian study on 212 TC patients receiving bleomycin-containing chemotherapy revealed bleomycin-induced pneumonitis (BIP) in 73 patients (34%) with the majority of these (75%) asymptomatic [341]. Granulocyte colony stimulating factor use was not associated with increased risk of BIP in multivariable analyses nor was it associated with increased severity of symptomatic BIP. There was a non-statistically significant trend towards greater risk of BIP in patients that developed renal impairment during chemotherapy treatment [341].

*8.2.5 **Cardiovascular toxicity***

Thromboembolic events (mostly venous) occur more frequently in GCT patients receiving chemotherapy than in other young male adults treated with chemotherapy for other cancers [226]. Low-dose heparins used during the course of chemotherapy may prevent the onset of thromboembolic events [234], though level 1 evidence is lacking. Mortality from cardiovascular disease (CVD) is higher in TCSs than in the general population (OR: 5) [227, 342, 343]. Furthermore, CVD is more common in chemotherapy-treated TCSs than in those who underwent surgery only [182, 344]. Feldman *et al.,* applied the Framingham Risk Score (FRS) on 787 TC survivors and compared the results with controls [345]: FRS did not differ by chemotherapy regimen (BEP 3 vs. EP 4) nor between control and TCSs, although the latter were three times less likely to smoke and generally

more physically active. However, less educated, and less vigorously active TCSs had higher FRS representing a high-risk subgroup for intense follow-up and counselling [345].

Most of the above studies are registry-based and thus limited. Lauritsen *et al.*, took advantage of the comprehensive prospective registration of cancer, diagnoses and drug prescription in Denmark comparing outcomes between 5,185 GCT patients and 51,850 men without GCT [227].

Cisplatin, etoposide, bleomycin (BEP) chemotherapy, applied in 1,819 GCT patients increased the risks of hypertension and hypercholesterolemia and thus CVD within one year after initiation of BEP: with hazard ratios (HRs) of 6.3, 6.0, and 24.7 for myocardial infarction, cerebrovascular accident, and venous thromboembolism, respectively. One year after BEP treatment, the risk of CVD decreased to normal levels, but after ten years, increasing risks were found for myocardial infarction (HR: 1.4; 95% CI: 1.0 to 2.0) and cardiovascular death (HR: 1.6; 95% CI: 1.0 to 2.5) [227].

Metabolic syndrome, a strong risk factor for CVD and its components, hypertension, obesity and hypercholesterolaemia, increases with treatment intensity (OR: 9.8) [343, 346, 347]. Hypogonadism increases the risk of insulin resistance, a proxy for metabolic syndrome, and an inherent risk of CVD. Bogefors *et al.*, showed, however, that most associations between TC treatment and metabolic parameters became statistically non-significant after adjustment for hypogonadism, indicating that hypogonadism might be the mediator of several toxicities which are usually attributed to the applied TC treatment [348]. Circulating residual serum platinum might exert endothelial stress and thereby possibly lead to hypertension [349]. Furthermore, exposure to circulating platinum is associated with paraesthesia, hypogonadism, and hypercholesterolaemia as well as major vascular events [234].

In a 30-year follow-up, chemotherapy treated TCSs used more often anti-hypertensive or lipid-lowering medications as controls. The TCSs' diastolic heart function was impaired as compared to the controls, whereas no difference was found regarding systolic- or valvular function or prevalence of arrhythmias [350]. The finding of increased vascular stiffness of TCSs more than 20 years after chemotherapy suggests accelerated vascular aging; thus, highlighting the need for intensive cardiovascular risk management [351].

Physical activity reduces the risk of metabolic syndrome and CVD. High-intensity aerobic interval training (HIIT) for twelve weeks improved cardiorespiratory fitness, multiple pathways of CVD risk, and surrogate markers of mortality in TCSs as compared to standard care, i.e., no supervised training [352]. However, HIIT during cisplatin-based chemotherapy might be harmful as a planned study on 94 patients was closed early after recruiting nineteen patients and the finding of severe CVD complications among three out of nine patients undergoing HIIT [353]. Two patients developed a pulmonary embolism (respectively at days seven and nine of BEP cycle 2) and the remainder a myocardial infarction (at day seven of BEP cycle 3). It is difficult to draw firm conclusions from such small patient numbers, but the observed CVD was well above the expected 5% risk of thromboembolic complications during or shortly after cisplatin-based chemotherapy such that the authors discourage HIIT during cisplatin-based chemotherapy for TC.

8.2.6 ***Raynaud-like phenomena, Neurotoxicity & Ototoxicity***

Chemotherapy-related Raynaud-like phenomena were reported before the introduction of cisplatin and are usually attributed to bleomycin [354, 355]. Cisplatin is believed to contribute to cold-induced vasospasms. Vogelzang *et al.,* reported that the incidence of Raynaud's phenomenon was higher after treatment with CVB than with vinblastine and bleomycin only, 41% vs. 21%, respectively [356].

Cisplatin induces a symmetric dose-dependent sensory, distal, length-dependent glove and stocking paraesthesia, affects 29% of TCSs who received cisplatin-based chemotherapy as opposed to 10% after orchidectomy alone [343, 357]. Treatment with five or more cycles increases the frequency of this symptom to 46%. Paclitaxel-induced acute neuropathy consists of an acute pain syndrome, which usually develops within three to seven days following its administration. Platinum is measurable in the serum of TCSs many years after its application with the intensity of paraesthesia more strongly associated with platinum serum level than with the cumulative dose of applied cisplatin [349]. Patients who experience a larger decline in circulating residual serum platinum during follow-up are at reduced risk of worsening of tinnitus or hand paraesthesia [358].

Cisplatin-induced ototoxicity comprises tinnitus and hearing impairment, particularly frequencies of 4,000 Hz and higher, and is caused by damage to the outer hair cells in the inner ear [343]. Encouragingly, hearing impairment deteriorated not considerably after the first decade after chemotherapy and quite normal speech perception tests 30 years after treatment indicated a limited clinical relevance of the high-frequency hearing

loss [359, 360]. Both hearing impairment and tinnitus are considerably increased after application of 50 mg/m^2 cisplatin over two days as compared to 20 mg/m^2 over five days (OR: 5.1 and 7.3, respectively), indicating a higher impact of serum peak concentrations than cumulative doses [357]. A significant association between Glutathione S-transferases (GST) genotypes and the risk of cisplatin-induced ototoxicity has been demonstrated [361, 362].

A comprehensive clinical and genome-wide analysis of multiple severe cisplatin-induced neurotoxicities has revealed a correlation between neurotoxicity, ototoxicity, and Raynaud phenomena in TCSs [363]. Of particular interest was the observation that certain TCSs seem to be particularly vulnerable to develop multiple and serious neuro-otological toxicities. TCSs without toxicities comprised the 196 controls and TCSs with two to three severe toxicities represented the 104 cases. Only three controls (1.5%) reported fair/poor health as compared to 18 (17.5%) of the cases.

Patients with multiple severe neurotoxicities were also more likely to report symptoms of peripheral motor neuropathy. Current smoking had a clearly negative impact on severe neurotoxicities. No genome-wide significant SNPs for developing severe cisplatin-induced neurotoxicities were identified. The authors concluded that metastatic TC patients with good-risk features should preferably be treated with 3 x BEP instead of 4 x EP in order to avoid neurotoxicities by the fourth cycle of cisplatin [363].

*8.2.7 **Cognitive function***

There are concerns that chemotherapy may reduce the cognitive function leading to “chemo-brain.” Amidi *et al.*, could show an alteration of brain structural networks after cisplatin-based chemotherapy for TC [364]. Impaired brain networks may underlie poorer performance over time on both specific and non-specific cognitive functions in TC survivors following chemotherapy.

*8.2.8 **Nephrotoxicity***

Cisplatin-based chemotherapy may lead to long-term renal dysfunction in 20-30% of TCSs [234, 344, 346]. In TC patients, reduced renal excretion of cisplatin and bleomycin might increase the risk of other toxicities, e.g., bleomycin-related pneumonitis [365, 366]. A comprehensive assessment of 1,206 Danish TCSs, however, did not reveal a significant association between chemotherapy-induced impaired renal function and other toxicities [342]. Renal recovery was poor after five or more cycles of BEP as compared to after BEP x 3 [347]. The estimation of glomerular filtration rate (eGFR) depends on whether creatinine or cystatin is applied, with the latter substance leading to an overestimation of eGFR in cisplatin treated TCSs, whereas this discrepancy was not found in patients with chronic kidney failure due to medical disease [367]. Genomic markers are related to the risk of cisplatin-induced nephrotoxicity [368]. How these results will impact selection and/or modification of chemotherapy remains to be seen.

*8.2.9 **Hypogonadism***

Testicular endocrine dysfunction comprises insufficient testosterone production and/or compensatory increased LH levels. Subnormal testosterone levels have been reported in TCSs treated with chemotherapy, when compared to those treated with surgery only or the general population [343, 365, 369, 370]. Compensated Leydig cell dysfunction in TCSs (testosterone within normal limits & increased LH values) was not associated with symptoms of depression, anxiety, sexual dysfunction, fatigue or impaired overall self-evaluated QoL, such that testosterone substitution seems not to be indicated in these patients [371].

Hypogonadism increases the risk of insulin resistance and hence the risk of metabolic syndrome, which, in turn, might lead to CVD in the long term [348]. Wiechno *et al.*, could show a decline in testosterone and an increase in LH and FSH within one year after treatment for unilateral TC [372]. Although there are clear indications of hypogonadism-related complications, and despite an established association between low testosterone and metabolic syndrome, no clear association between Leydig cell dysfunction and the risk of metabolic syndrome during a median ten-year follow-up could be established [373].

Walsh *et al.*, reported a RCT demonstrating a benefit of testosterone replacement therapy in young male survivors of TC, lymphoma, and leukaemia aged 25–50 years who had low morning serum testosterone. Under the six months of replacement therapy, cancer survivors that received testosterone experienced a decrease in trunk fat mass and whole-body fat mass and an increase in lean-body mass, but no effect on reported physical functioning or other QoL scores when compared to those that received a placebo gel [374]. The absence of improved QoL and the issue of rendering TCSs sub- or infertile by testosterone replacement therapy is the reason why the TC panel does not recommend this strategy until more compelling endpoints are reported. An ongoing Danish RCT might yield new level 1 evidence [375].

Erectile dysfunction (OR: 4.2) has been significantly associated with chemotherapy in a recent multicentre study [343]. Of 481 North American TCSs treated with modern cisplatin-based chemotherapy, 38% were hypogonadal (defined as on testosterone substitution or serum testosterone level ≤ 3.0 ng/mL) [376]. Hypogonadism was associated with the number of adverse health outcomes and its risk increased with age and obesity [377].

*8.2.10 **Fatigue***

Chronic fatigue (CF) is described as a subjective feeling of emotional, physical and/or cognitive tiredness that is not relieved by rest and persists for more than six months. Significantly higher levels of C-reactive protein and interleukin-1 receptor antagonist are measured in TCSs with CF [377]. Also, a significantly higher frequency of CF (16%) was reported in a cross-sectional Norwegian study of long-term TCSs at a median of twelve years after treatment for TC when compared with the age-matched Norwegian population (10%) [210]. Of note, the prevalence of CF increased from 15-27% during a ten-year period in long-term TCSs [378].

*8.2.11 **Quality of life***

Quality of life is transiently reduced by chemotherapy, during which patients experience a loss of appetite, increased fatigue, increased dyspnoea and reduced social- and physical function [210]. When comparing three or four cycles of BEP in good-risk patients, all outcomes favour treatment with three courses [209]. After one and two years, one-third of patients reported an improvement in global QoL after chemotherapy, while one fifth of patients reported deterioration, with no difference between treatment groups. After adjuvant treatment of non-seminoma stage I patients, there was no difference in short-term or long-term (five years) QoL between RPLND, or one course of BEP [181].

Anxiety, depression, fear of cancer recurrence (FCR), and distress may impair the health-related quality of life (HRQoL) in TCSs. A recent review identified a considerable variation in both severity and prevalence of each of these issues, probably due to use of different questionnaires and also cultural variations [379]. Clinically significant anxiety is reported in approximately one out of five TCSs and distress in one out of seven; therefore, it is more frequent among TCS than in the general population. Depression was not uniformly found to be more frequent, whereas every third TCSs reported fear of recurrence. Importantly, poorer psychological outcomes were more common among single, unemployed TCSs with a low socio-economic status and co-morbidities, as well as those experiencing worse symptoms/side effects, and those using passive coping strategies.

A German study found clinically significant anxiety in 6.1% and depression present in 7.9% of TC patients, with both a higher number of physical symptoms and the prospect of having children being related to higher levels of anxiety and depression [380].

Among 2,479 Danish long-term TCSs, higher anxiety was reported by those who experienced bilateral TC as compared to unilateral TC [381]. For a subset of approximately 11% of TCSs, the diagnosis of TC was traumatic. This subset was found to suffer from post-traumatic stress disorder in the long term, which resulted in significant QoL reduction [382]. Kreiberg *et al.,* recommend stress symptoms at follow-up visits in order to timely identifyTCSs requiring support [383]. This recommendation is supported by the finding of an increased mental health service utilisation as compared to healthy controls [384]. Testicular cancer survivors who developed bilateral TC had a higher degree of anxiety compared to survivors of unilateral TC but did not report otherwise impaired QoL [385].

Erectile dysfunction was found in men who underwent radiotherapy, BEP chemotherapy with subsequent surgical resection of residual masses, or more than one line of treatment. The latter group also reported orgasmic dysfunction. After radiotherapy, significantly more men reported overall decreased sexual satisfaction, whereas all other groups reported no difference in overall satisfaction, intercourse satisfaction, and sexual desire [385].

Testicular cancer survivors were more likely to have high levels of stress compared to the reference population with a prevalence ratio of 1.56 (95% CI: 1.40 – 1.73), according to a big cohort study with 2,252 patients, with a median of nineteen years from diagnosis [383].

9. RARE ADULT PARA- AND TESTICULAR TUMOURS

Less than 5% of testicular cancers are unrelated to GCNIS and lack 12p alterations [386, 347]. These tumours are rare with available literature based on case reports and small retrospective series. Given the rarity of non-germ cell para-/testicular cancers, referral of these cases to specialist units for multidisciplinary discussion including central image and pathology review is highly recommended. As a result of publication bias related to these types of study, the risk of metastatic disease may be less than that reported in the literature.

9.1 Classification

These testicular tumours have a similar presentation as TC and are only identified after histopathologic examination. They are classified according to the WHO Classification of Tumours of the Urinary System and Male Genital Organs [387].

9.2 Spermatocytic Tumours

Spermatocytic tumours are GCTs unrelated to GCNIS. They show a unique amplification of chromosome 9 corresponding to the DMRT1 gene and are never associated with other forms of germ cell tumours [387].

Spermatocytic tumours are rare, occur exclusively in the testis and do not normally show elevated tumour markers [387]. Previously named “spermatocytic seminomas” they have been recently reclassified as spermatocytic tumours [387]. As those tumours cannot be differentiated from seminoma GCT by frozen section analysis, radical orchiectomy is the standard treatment option. Outcomes after testis-sparing surgery or adjuvant treatment is unknown and therefore not recommended [388]. Metastatic disease is very rare and typically presents at or soon after initial diagnosis with limited survival [388].

9.3 Sex cord-stromal tumours

Sex cord–stromal tumours are relatively uncommon but represent the second largest group of primary testicular tumours after GCT’s [389]. As a small subset of these tumours are clinically malignant, a thorough evaluation of those morphological features associated with malignancy should be performed to guide management. Two or more of the following features are associated with malignant potential: size > 5 cm, infiltrative borders, cytological atypia, three or more mitotic figures per ten high-power fields, vascular invasion and necrosis [389].

*9.3.1 **Leydig cell tumours***

Leydig cell tumours comprise about 4% of adult testicular tumours. These mainly present as localised tumours with metastases occurring in only 2.5% [390]. They may present with hormonal manifestations, including gynaecomastia and more rarely are accompanied by Cushing’s Syndrome [389]. With testis-sparing surgery a local recurrence rate of 7% has been reported although no adjuvant treatment options can be recommended [391]. Several risk factors for metastatic disease have been proposed which may guide image-guided follow-up intensity [391]. Survival of men with metastatic disease is poor but occasional responses to surgical and systemic treatment have been reported [391].

*9.3.2 **Sertoli cell tumours***

Sertoli cell tumours account for approximately 1% of testicular neoplasms [389]. The risk of metastases is unclear. With testis-sparing surgery a local recurrence rate of < 1% has been reported although no adjuvant treatment options can be recommended [392]. Several risk factors for metastatic disease have been proposed which may guide image guided follow-up intensity [392]. Survival of men with metastatic disease is poor although response to surgery has been occasionally reported [392].

*9.3.3 **Granulosa cell tumour***

Granulosa cell tumours, which include adult and juvenile variants, are extremely rare and metastatic potential is unclear [389]. With testis-sparing surgery a local recurrence rate of 5% has been reported although no adjuvant treatment options can be recommended [393]. Whereas metastatic disease has never been reported in juvenile granulosa cell tumours, men with adult type may occasionally present with metastatic disease [393]. Survival of men with metastatic disease is poor although rare instances of response to surgical or systemic treatment has been reported [393].

*9.3.4 **Thecoma/fibroma group of tumours***

These tumours derive from the testicular parenchymal stroma or from the tunica albuginea. They seem to be uniformly benign [389, 394].

*9.3.5 **Paratesticular tumours of the epididymis or spermatic cord***

The majority of epididymal masses are benign cystic or inflammatory conditions. Solid epididymal tumours are rare and comprise numerous benign and neoplastic lesions. In the only population-based analyses [395], the majority of neoplastic lesions of the epididymis or spermatic cord were sarcomas, metastases from other organs or primary adenocarcinomas similar to proportions reported in institutional studies [396, 397]. Benign lesions, which may comprise the majority in clinical practice include lipomas, adenomatoid tumours leiomyomas and papillary cystadenomas.

Robust criteria to differentiate between neoplastic benign lesions have not been defined although ultrasonography with or without fine needle aspiration [398] MRI [49, 399] or surgical exploration with frozen section analyses or histopathological confirmation can be considered. No clear recommendation can be provided regarding surgical approach, extent of resection and neo- or adjuvant treatment can be given.

9.4 Mesothelioma of the tunica vaginalis testis

Mesothelioma of the tunica vaginalis testis is a rare but aggressive disease [400]. Beside older age, larger tumour size, presence of necrosis, angiolymphatic invasion or a high mitotic index the only modifiable risk factors represents local recurrence. Therefore, aggressive local treatment with hemiscrotectomy is recommended. No clear recommendation can be given regarding adjuvant treatment. In case of metastatic disease, the median overall survival is a few months only and multimodal treatment could be considered.

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11. CONFLICT OF INTEREST

All members of the Testicular Cancer Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines.

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12. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on Thromboprophylaxis in Urological Surgery

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1. INTRODUCTION

1.1 Aims and objectives

Due to the hypercoagulable state induced by surgery, serious complications of urological surgery include deep vein thrombosis (DVT) and pulmonary embolism (PE) - together referred to as venous thromboembolism (VTE) - and major bleeding [1-4]. Decisions regarding pharmacologic thromboprophylaxis in urologic surgery involve a trade-off between decreased risk of (VTE) and increased risk of bleeding [1-3]. Currently, there exists substantial practice variation in the use of thromboprophylaxis in urology, both within and between countries [5-7]. This variation is unsurprising when one considers that recommendations from national and international guidelines often conflict [2].

To date, existing recommendations for thromboprophylaxis have been limited by a lack of urology-specific evidence [2]. Decisions regarding thromboprophylaxis require both estimates of relative effects on VTE and bleeding, and absolute risks of VTE and bleeding in the absence of prophylaxis (the latter is refered to as baseline risk). Substantial evidence from randomised control trials (RCTs) across a range of surgical procedures is available, and it is reasonable to assume that relative effects of prophylaxis are similar across surgical procedures. Evidence regarding baseline risk across urological procedures is, however, more limited, and systematic summaries of the available evidence have thus far been unavailable [1, 3].

To develop these guidelines, the Panel conducted systematic reviews of the baseline risk of VTE and bleeding in a wide variety of urological procedures [1, 8, 9]. These reviews provide a stronger evidence base for urological thromboprophylaxis guidelines than has been previously available.

Utilising this newly summarised evidence [8, 9], these Guidelines from the European Association of Urology (EAU) Working Panel on Thromboprophylaxis in Urological Surgery provide practical evidence-based guidance regarding post-surgery thromboprophylaxis and peri-operative management of antithrombotic agents in urology.

Clinicians who wish to implement our recommendations should bear in mind that guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to guide decisions that must also take into account patients' values and preferences as well as their individual circumstances. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Guidelines on Thromboprophylaxis in Urological Surgery Panel consists of physicians/methodologists with expertise from urology, internal medicine, haematology, gynaecology and clinical epidemiology. Although the Guidelines are written primarily for urologists, they can also be used by other physicians, patients or other interested parties.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Thromboprophylaxis in Urological Surgery Guidelines. These are abridged versions which may require consultation together with the full text version. All are available through the EAU website: http://www.uroweb.org/guidelines/.

1.4 Publication history

These EAU Guidelines on Thromboprophylaxis in Urological Surgery are the first of their kind.

2. METHODS

2.1 Guideline methodology

The EAU Guidelines on Thromboprophylaxis in Urological Surgery Panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessment of quality of evidence and grading of recommendations [10-12].

GRADE offers four levels of evidence quality, reflecting the degree of certainty or confidence in the evidence: high, moderate, low, and very low [11]. For relative treatment effect, RCTs are high-quality evidence

and observational studies are low-quality evidence. For baseline risk (such as risk of VTE post-surgery), observational studies are high-quality evidence. Quality may be rated down as a result of limitations in study design or implementation (risk of bias), imprecision of estimates (wide confidence intervals), inconsistency (variability in results), indirectness of evidence, or publication bias. Quality may be rated up on the basis of a very large magnitude of effect, a dose-response gradient, and if consideration of all plausible biases would reduce an apparent treatment effect, or create an effect when none is apparent. The lowest quality of any critical outcome represents the overall quality of evidence.

The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects. GRADE classifies recommendations as strong or weak [12]. Strong recommendations mean that all or virtually all informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly. Weak recommendations mean that patients' choices will vary according to their values and preferences, and that clinicians must ensure that patients' care is in keeping with their values and preferences through shared decision-making. Strength of recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence (certainty in estimates), and nature and variability of values and preferences.

Post-operative thromboprophylaxis and peri-operative management of antithrombotic agents in urology are discussed seperately. Specific methods are presented in the context of the relevant recommendations.

3. GUIDELINE

3.1 Thromboprophylaxis post-surgery

*3.1.1 **Introduction***

This guideline provides procedure and patient risk-specific guidance weighing the benefit of reduced VTE with the harm of increased bleeding. The Panel provides recommendations for numerous urologic procedures with a simple and practical patient risk stratification scheme.

*3.1.2 **Outcomes and definitions***

The Panel defined non-fatal and fatal symptomatic VTE and non-fatal and fatal major bleeding as key outcomes. Venous thromboembolism was defined as symptomatic DVT or PE and major bleeding was defined as bleeding requiring re-operation or intervention (such as angioembolisation). Transfusion, indwelling catheter, or change in hemoglobin levels were not considered as part of "major bleeding".

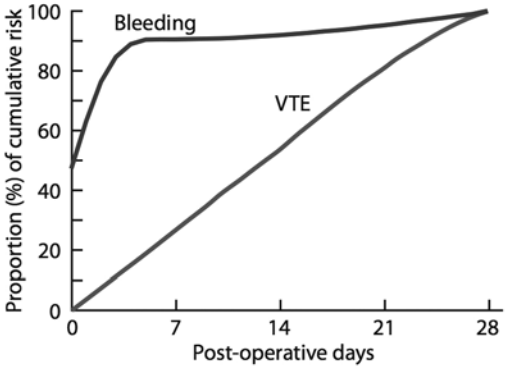
*3.1.3 **Timing and duration of thromboprophylaxis***

High-quality evidence suggests that, of the cumulative risk during the first four weeks post-surgery, approximately 50% of major bleeds occur between surgery and the next morning and approximately 90% during the first four post-surgical days. In contrast, the risk of VTE is almost constant during these first four post-surgical weeks (Figure 1) [1, 13-15].

There are no direct comparisons of the same agent administered before versus after surgery. Recent studies with direct-acting oral anticoagulants (DOACs) in orthopedic surgery have, however, suggested that, relative to starting low molecular weight heparin (LMWH) before surgery, prophylaxis can begin 24 hours after surgery without an increase in VTE but with a decrease in bleeding complications [16, 17]. Given these findings, in addition to the compelling rationale regarding the relative timing of bleeds versus thrombosis (Figure 1), we recommend administration of thromboprophylaxis beginning the day after surgery.

One could argue that prophylaxis be started even later than this, especially in procedures with high bleeding risk. The extent to which an even later start would decrease the effectiveness of thromboprophylaxis is, however, open to question. Given that the further the patient is from surgery the greater the net benefit of prophylaxis (as bleeding risks decreases), while the risk of VTE is just as great in the fourth week after surgery as in the first, the optimal duration of pharmacological prophylaxis is approximately four weeks post-surgery [1, 13-15].

Figure 1: Proportion of cumulative risk (%) of VTE and major bleeding by week since surgery during the first four post-operative weeks



	Proportion of 28-day cumulative bleeding risk
Operation day	47.4%
Post-operative day 1	63.3%
Post-operative day 2	76.6%
Post-operative day 3	84.9%
Post-operative day 4	89.2%
Post-operative day 28	100.0%

Figure modified from: Tikkinen KA, *et al.* Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. *Syst Rev* 2014;3:150. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

*3.1.4 **Basic principles for recommending (or not recommending) post-surgery thromboprophylaxis***

Considerations in the administration of thromboprophylaxis include the relative effect of prophylaxis on key outcomes, baseline risk of key outcomes, as well as patient-related risk (and protective) factors. Finally, one must consider the quality of evidence (certainty in estimates) as well as the relative importance of the relevant outcomes.

3.1.4.1 Effect of prophylaxis on key outcomes

The Panel performed several meta-analyses of RCTs in urology, general surgery, gynecology, and gastrointestinal surgery to inform relative risk estimates of thromboprophylaxis [1, 8, 9]. These meta-analyses demonstrated that anticoagulants (such as LMWH) reduce the relative risk of VTE by approximately 50% and increase the relative risk of major bleeding by approximately 50% [1, 8, 9]. These meta-analyses also demonstrated 50% VTE risk reduction for mechanical prophylaxis [1, 8, 9]. An earlier meta-analysis informing the risk estimates for direct-acting oral anticoagulants yielded similar estimates: a decrease in the relative risk of VTE by approximately 50% and an increase of major bleeding by approximately 50% [18]. The evidence regarding pharmacological prophylaxis was judged as high-quality but low-certainty for mechanical prophylaxis because studies used surrogate outcomes, had very few events, unblinded patients and assessors, and provided almost no information on intermittent pneumatic compression (low-quality evidence) [1, 8, 9].

3.1.4.2 Baseline risk of key outcomes

The Panel performed a series of systematic reviews to provide estimates of absolute risk of symptomatic VTE and bleeding requiring re-operation in urologic surgery [1, 8, 9]. The cited publications, with minor modifications, provide the evidence summary used to develop these recommendations.

3.1.4.3 Patient-related risk (and protective) factors

The Panel conducted a comprehensive literature search addressing VTE and bleeding risk factors in the context of urology, general surgery, gynecology, and gastro intestinal surgery [1]. A model was developed for VTE risk based on the studies reporting the most relevant and high-quality evidence [19-27] (Table 1). However, this model has not been validated and clinicians may consider other factors, including the length of the surgical procedure, oral contraception, immobility, spinal cord injury, and inheritable blood disorders such as

antiphospholipid antibody syndromes, factor V Leiden, antithrombin, protein C or S deficiencies, when making decisions. The Panel's search did not reveal studies demonstrating convincing and replicable risk factors for bleeding [1]; therefore, bleeding risk was not stratified by patient specific factors.

Table 1: Venous thromboembolism (VTE) according to patient risk factors

	Risk	Likelihood of VTE
Low risk	No risk factors	1x
Medium risk	Any one of the following: age 75 years or more; Body mass index 35 or more; VTE in 1st degree relative (parent, full sibling, or child).	2x
High risk	Prior VTE Patients with any combination of two or more risk factors	4x

3.1.4.4 From evidence to recommendations

When creating recommendations, the Panel first calculated the net benefit (absolute reduction in VTE risk – absolute increase in bleeding risk) and thereafter considered quality of evidence, separately for both pharmacological and mechanical prophylaxis. The Panel made strong recommendations only if the quality of evidence was moderate or high and net benefit fulfilled threshold criteria (see below); otherwise, the Panel made weak recommendations.

When calculating the net benefit, twice the weight was assigned for major bleeding as for 'any symptomatic VTE'. The most comprehensive guideline published in the field, the American College of Chest Physicians (ACCP) guideline on "Prevention of VTE in Nonorthopedic Surgical Patients" considered symptomatic VTE and major bleeding as having the same weight. However, they included transfusions in their definition of major bleeding [28] which the Panel considered less relevant because: 1) studies often did not report transfusions, 2) criteria for transfusion vary widely between studies, and use of transfusion may have limited relation to underlying bleeding, and 3) transfusions are less important to patients than are reoperations. Given this guideline's focus on only the more severe bleeds – those that require re-operation – the greater weight on preventing bleeding is appropriate.

For each procedure (and separately for each patient risk factor stratum), the net benefit of using pharmacological thromboprophylaxis (benefit from VTE reduction – harm from bleeding) was calculated. After considering the net benefit and quality of evidence, the thresholds presented in Table 2 were indentified.

Table 2: Thresholds of net benefit and quality of evidence used when creating recommendations

Net benefit*	Recommendation	Note
Pharmacological prophylaxis		
≥ 10 per 1000	STRONG in FAVOUR	If based on moderate or high-quality evidence
≥ 10 per 1000	WEAK in FAVOUR	If based on low or very low-quality evidence
≥ 5-10 per 1000	WEAK in FAVOUR	In borderline situations prophylaxis was always favoured as case fatality is higher for VTE than for bleeding [8, 9]
≥ 1-5 per 1000	WEAK AGAINST	
< 1 per 1000	WEAK AGAINST	If based on low or very low-quality evidence
< 1 per 1000	STRONG AGAINST	If based on moderate or high-quality evidence
Mechanical prophylaxis		
≥ 2.5 per 1000	WEAK in FAVOUR	
< 2.5 per 1000	WEAK AGAINST	

* Net benefit is equal to absolute reduction in VTE risk minus absolute increase in bleeding risk (with twice the weight for major bleeding as for VTE). The net benefit is positive when the value of reduced VTE is greater than increased bleeding.

These thresholds reflect value and preference considerations for which there is limited evidence available [29]. A recent multinational study found that the median threshold net benefit at which women with a history of VTE were willing to accept use of heparin to prevent VTE during pregnancy or the post-partum period is 30 in 1,000 [30]. In that study, the use of prophylaxis spanned the entire duration of pregnancy and continued during the

post-partum period. As post-surgery prophylaxis has a much shorter duration, and is thus less burdensome, our threshold of strong recommendation when net benefit is 10 in 1,000 or more is consistent with this evidence. As mechanical prophylaxis is typically used for a shorter duration than the Panel recommend for pharmacological prophylaxis [31], a lower threshold for mechanical prophylaxis was used.

Making a recommendation regarding thromboprophylaxis requires trading off VTE reduction against bleeding increase, and thus placing a relative value on the two events. A serious bleed (defined as bleeding requiring re-operation or intervention) was considered twice as important as a VTE (defined as symptomatic DVT or PE) event. For patients who feel very differently about this relative value judgment, the Panel's recommendations may not be optimal.

3.1.5 General statements for all procedure-specific recommendations

Consistent with GRADE guidance [32], a single good practice statement was made in which the supporting evidence is compelling, though indirect, and which was not summarised systematically. This association between early ambulation and decreased post-operative complications, in particular decrease in VTE, and early discharge from hospital is convincing. Further, early ambulation has no important adverse consequences. Therefore, the Panel believes that early ambulation for all patients after surgery represents good clinical practice.

The following apply to all recommendations for pharmacologic prophylaxis:

- All recommendations are based on a starting time of the morning after surgery.
- The optimal duration of prophylaxis for all recommendations is approximately four weeks post-surgery.
- There are number of acceptable alternatives for pharmacologic prophylaxis (Table 3).

Table 3: Alternative regimens for pharmacological prophylaxis

Pharmacological agent	Dosage*
Low molecular weight heparins:	
Dalteparin	5,000 IU injection once a day
Enoxaparin	40 mg injection once a day
Tinzaparin	3,500/4,500 IU injection once a day
Unfractionated heparin	5,000 IU injection two or three times a day
Fondaparinux†	2.5 mg injection once a day
Direct acting oral anticoagulants†:	
Dabigatran	220 mg tablet once a day
Apixaban	2.5 mg tablet once a day
Edoxaban	30 mg tablet once a day
Rivaroxaban	10 mg tablet once a day

** Dosages may not apply in renal impairment.*

† Fondaparinux and direct acting oral anticoagulants have not been sufficiently studied in urology to warrant on-label use for post-surgery thromboprophylaxis.

3.1.6 Recommendations

Ambulatory day surgery

R1. In all patients undergoing minor ambulatory day surgery (for example, circumcision, hydrocelectomy and vasectomy), the Panel recommends against use of pharmacological prophylaxis (***strong, moderate-quality evidence***), and against use of mechanical prophylaxis (***strong, moderate-quality evidence***).

Note: The Panel is of the opinion that these patients have risk of VTE close to the general population with an increased risk of bleeding.

Open radical cystectomy

R2. In all patients undergoing open radical cystectomy, the Panel recommends use of pharmacological prophylaxis (***strong, moderate or high-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Robotic radical cystectomy

R3. In all patients undergoing robotic radical cystectomy, the Panel suggests use of pharmacological prophylaxis (***weak, low-quality evidence***), and suggest use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Table 4: Procedure-specific evidence summaries with recommendations for radical cystectomies

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Cystectomy, Open	Venous thromboembolism	Low-risk	29	13	Moderate	Strong, for	Weak, for
		Medium-risk	58	27	High	Strong, for	Weak, for
		High risk	116	56	High	Strong, for	Weak, for
	Bleeding requiring reoperation		3.0		Moderate/ High		
Cystectomy, Robotic	Venous thromboembolism	Low-risk	26	11	Low	Weak, for	Weak, for
		Medium-risk	52	24	Low	Weak, for	Weak, for
		High risk	103	50	Low	Weak, for	Weak, for
	Bleeding requiring reoperation		3.0		Low		

* Net benefit is equal to absolute reduction in VTE risk minus absolute increase in bleeding risk (with twice the weight for major bleeding as for VTE). For instance, in medium-risk patients undergoing open radical cystectomy, use of pharmacological prophylaxis, such as LMWH, beginning first post-surgery day for four weeks decreases absolute risk of VTE by 29 per 1,000 and increases absolute risk of bleeding by 0.8 per 1,000 (Figure 1). As twice the weight for major bleeding was assigned as for VTE, the net benefit is 27 per 1,000.

Laparoscopic radical prostatectomy

R4. For patients undergoing laparoscopic radical prostatectomy without pelvic lymph node dissection (PLND), for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***) and suggests against use of mechanical prophylaxis (***weak, low-quality evidence***); for those at moderate and high risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate or high quality evidence***) and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R5. For patients undergoing laparoscopic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R6. For patients undergoing laparoscopic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (***weak, high-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Open radical prostatectomy

R7. For patients undergoing open radical prostatectomy without PLND or with standard PLND, for those at low risk of VTE, the use of pharmacologic prophylaxis is suggested (***weak, moderate-quality evidence***); for those at medium and high risk, the use of pharmacologic prophylaxis is recommended (***strong, moderate or high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R8. For all patients undergoing open radical prostatectomy with extended PLND, the Panel recommends use of pharmacologic prophylaxis (***strong, moderate or high-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Robotic radical prostatectomy

R9. For patients undergoing robotic radical prostatectomy without PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***) and suggests against use of mechanical prophylaxis (***weak, low-quality evidence***); for those at medium and high risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***) and suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R10. For patients undergoing robotic radical prostatectomy with standard PLND, for those at low risk of VTE, the Panel recommends against use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); for those at medium risk, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R11. For patients undergoing robotic radical prostatectomy with extended PLND, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

Table 5: Procedure-specific evidence summaries with recommendations for radical prostatectomies

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharmacological prophylaxis*	Certainty in estimate	Recommendations for pharmacological prophylaxis	Recommendations for mechanical prophylaxis
Prostatectomy, Laparoscopic without pelvic lymph node dissection (PLND)	Venous thromboembolism	Low-risk	4.0	-1.7	Moderate	Strong - against	Weak – against
		Medium-risk	8.0	0.30	Moderate	Weak - against	Weak - for
		High-risk	15	4.0	High	Weak - against	Weak - for
	Bleeding requiring reoperation		7.0		Moderate		
Prostatectomy, Laparoscopic with standard PLND	Venous thromboembolism	Low-risk	8.0	-1.3	Moderate	Strong - against	Weak - for
		Medium-risk	15	2.2	Moderate	Weak - against	Weak - for
		High-risk	30	10	High	Strong - for	Weak - for
	Bleeding requiring reoperation		10		Moderate		
Prostatectomy, Laparoscopic with extended PLND	Venous thromboembolism	Low-risk	15	0.10	Moderate	Weak - against	Weak - for
		Medium-risk	30	7.6	High	Weak - for	Weak - for
		High-risk	60	23	High	Strong - for	Weak - for
	Bleeding requiring reoperation		14		Moderate		
Prostatectomy, Open without PLND	Venous thromboembolism	Low-risk	10	4.5	Moderate	Weak - for	Weak - for
		Medium-risk	20	9.5	Moderate	Strong - for	Weak – for
		High-risk	39	19	High	Strong - for	Weak - for
	Bleeding requiring reoperation		1.0		Moderate		

Prostatectomy, Open with standard PLND	Venous thrombo-embolism	Low-risk	20	8.9	Moderate	Weak – for	Weak - for
		Medium-risk	39	18	High	Strong - for	Weak - for
		High-risk	79	38	High	Strong -for	Weak - for
	Bleeding requiring reoperation		2.0		Moderate		
Prostatectomy, Open with extended PLND	Venous thrombo-embolism	Low-risk	39	18	Moderate	Strong - for	Weak - for
		Medium-risk	79	38	High	Strong - for	Weak - for
		High-risk	157	77	High	Strong - for	Weak - for
	Bleeding requiring reoperation		2.0		Moderate		
Prostatectomy, Robotic without PLND	Venous thrombo-embolism	Low-risk	2.0	-1.1	Moderate	Strong - against	Weak - against
		Medium-risk	5.0	0.40	Moderate	Weak - against	Weak - for
		High-risk	9.0	2.4	Moderate	Weak - against	Weak - for
	Bleeding requiring reoperation		4.0		Moderate		
Prostatectomy, Robotic with standard PLND	Venous thrombo-embolism	Low-risk	5.0	-0.7	Moderate	Strong - against	Weak - for
		Medium-risk	9.0	1.3	Moderate	Weak - against	Weak - for
		High-risk	19	6.3	Moderate	Weak - for	Weak - for
	Bleeding requiring reoperation		6.0		Moderate		
Prostatectomy, Robotic with extended PLND	Venous thrombo-embolism	Low-risk	9.0	0.3	Moderate	Weak - against	Weak - for
		Medium-risk	19	5.3	Moderate	Weak - for	Weak - for
		High-risk	37	14	Moderate	Strong - for	Weak - for
	Bleeding requiring reoperation		8.0		Moderate		

Nephrectomy

R12. For patients undergoing laparoscopic partial nephrectomy, for those at low and medium-risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, low-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, moderate-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R13. For all patients undergoing open partial nephrectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

R14. For patients undergoing robotic partial nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at medium risk, the Panel suggests use of pharmacologic prophylaxis (***weak, moderate-quality evidence***); for those at high risk, the Panel recommends use of pharmacologic prophylaxis (***strong, high-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R15. For patients undergoing laparoscopic radical nephrectomy, for those at low or medium risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at high risk, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

R16. For patients undergoing open radical nephrectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***); and for all patients, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R17. For all patients undergoing radical nephrectomy with thrombectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

R18. For all patients undergoing open nephroureterectomy, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

Table 6: Procedure-specific evidence summaries with recommendations for kidney procedures for cancer

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharma-cological prophylaxis*	Certainty in estimate	Recommendations for pharma-cological prophylaxis	Recommendations for mechanical prophylaxis
Nephrectomy, Laparoscopic partial	Venous thrombo-embolism	Low-risk	11	-3.4	Low	Weak - against	Weak – for
		Medium-risk	21	1.6	Low	Weak - against	Weak – for
		High-risk	42	12	Moderate	Strong - for	Weak - for
	Bleeding requiring reoperation		17		Low/ Moderate		
Nephrectomy, Open partial	Venous thrombo-embolism	Low-risk	10	4.5	Very low	Weak - for	Weak – for
		Medium-risk	20	9.5	Very low	Weak - for	Weak – for
		High-risk	39	19	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Moderate		
Nephrectomy-Robotic partial	Venous thrombo-embolism	Low-risk	10	2.4	Moderate	Weak - against	Weak – for
		Medium-risk	19	6.9	Moderate	Weak - for	Weak – for
		High-risk	39	17	high-quality	Strong - for	Weak - for
	Bleeding requiring reoperation		5.0		Moderate		
Nephrectomy, Laparoscopic radical	Venous thrombo-embolism	Low-risk	7.0	0.9	Very low	Weak - against	Weak – for
		Medium-risk	13	3.9	Very low	Weak - against	Weak – for
		High-risk	26	10	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		5.0		Very low		
Nephrectomy, Open radical	Venous thrombo-embolism	Low-risk	11	5.2	Low	Weak - for	Weak – for
		Medium-risk	22	11	Low	Weak - for	Weak – for
		High-risk	44	22	Low	Weak - for	Weak - for
	Bleeding requiring reoperation		0.5		Very low		
Radical nephrec-tomy with thrombec-tomy	Venous thrombo-embolism	Low-risk	29	4.0	Very low	Weak - for	Weak - for
		Medium-risk	58	19	Very low	Weak - for	Weak - for
		High-risk	116	48	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		20		Very low		
Open nephro-ureterectomy	Venous thrombo-embolism	Low-risk	16	7.7	Very low	Weak - for	Weak - for
		Medium-risk	31	15	Very low	Weak - for	Weak - for
		High-risk	62	31	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		0.5		Very low		

R19. For all patients undergoing primary nerve sparing RPLND, the Panel suggests use of pharmacologic prophylaxis (***weak, very low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

Table 7: Procedure-specific evidence summaries with recommendations for primary nerve sparing retroperitoneal lymph node dissection

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharma-cological prophylaxis*	Certainty in estimate	Recommendations for pharma-cological prophylaxis	Recommendations for mechanical prophylaxis
Primary nerve sparing retroperitoneal lymph node dissection	Venous thrombo-embolism	Low-risk	23	10	Very low	Weak - for	Weak – for
		Medium-risk	45	21	Very low	Weak - for	Weak – for
		High-risk	91	44	Very low	Weak - for	Weak - for
	Bleeding requiring reoperation		2.0		Very low		

Non-cancer urological procedures

R20. For all patients undergoing transurethral resection of the prostate (TURP) or equivalent procedures, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (***weak, low-quality evidence***); and for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, low-quality evidence***).

R21. For patients undergoing laparoscopic donor nephrectomy or open donor nephrectomy, for those at low risk of VTE, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low or low-quality evidence***), and suggests against use of mechanical prophylaxis (***weak, very low or low-quality evidence***); for medium risk patients, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low or low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low or low-quality evidence***); and for high risk patients, the Panel suggests use of pharmacologic prophylaxis (***weak, very low or low-quality evidence***), and suggests use of mechanical prophylaxis until ambulation (***weak, very low or low-quality evidence***).

R22. For all patients undergoing open prolapse surgery or reconstructive pelvic surgery, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (***weak, very low or low-quality evidence***); while for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, very low or low-quality evidence***).

R23. For all patients undergoing percutaneous nephrolithotomy, the Panel suggests against use of pharmacologic prophylaxis (***weak, very low-quality evidence***); for those at low or medium risk of VTE, the Panel suggests against use of mechanical prophylaxis (***weak, very low-quality evidence***); while for those at high risk, the Panel suggests use of mechanical prophylaxis until ambulation (***weak, very low-quality evidence***).

Table 8: Procedure-specific evidence summaries (with recommendations) for non-cancer procedures

Procedure	Outcome	Baseline risk among 1000 patients		Net benefit per 1000 patients with pharma-cological prophylaxis*	Certainty in estimate	Recommendations for pharma-cological prophylaxis	Recommendations for mechanical prophylaxis
Transurethral resection of the prostate (TURP) or equivalent	Venous thrombo-embolism	Low-risk	2.0	-0.1	Low	Weak - against	Weak - against
		Medium-risk	4.0	0.9	Low	Weak - against	Weak - against
		High-risk	8.0	2.9	Low	Weak - against	Weak - for
	Bleeding requiring reoperation		2.0		Very low		
Donor nephrectomy, laparoscopic	Venous thrombo-embolism	Low-risk	4.0	1.5	Low	Weak - against	Weak – against
		Medium-risk	7.0	3.0	Low	Weak - against	Weak – for
		High-risk	14	6.5	Low	Weak - for	Weak - for
	Bleeding requiring reoperation		1.0		Low		
Donor nephrectomy, open	Venous thrombo-embolism	Low-risk	3.0	1.0	Very low	Weak - against	Weak – against
		Medium-risk	7.0	3.0	Very low	Weak - against	Weak – for
		High-risk	13	6.0	Very low	Weak - for	Weak – for
	Bleeding requiring reoperation		1.0		Very low		
Recipient nephrectomy, open	Venous thrombo-embolism	Low-risk	13	-5.6	Very low	Weak - against*	Weak - for
		Medium-risk	27	1.4	Very low	Weak - against*	Weak – for
		High-risk	53	14	Very low	Weak – for*	Weak - for
	Bleeding requiring reoperation		23		Very low		
Prolapse surgery, open	Venous thrombo-embolism	Low-risk	2.0	-1.1	Low	Weak - against	Weak – against
		Medium-risk	3.0	-0.6	Low	Weak - against	Weak – against
		High-risk	7.0	1.4	Low	Weak - against	Weak – for
	Bleeding requiring reoperation		4.0		Very low		
Reconstructive pelvic surgery (including sling surgery for stress urinary incontinence and vaginal prolapse surgery)	Venous thrombo-embolism	Low-risk	1.0	-1.1	Very low	Weak - against	Weak – against
		Medium-risk	3.0	-0.1	Very low	Weak - against	Weak – against
		High-risk	5.0	0.9	Very low	Weak - against	Weak - for
	Bleeding requiring reoperation		3.0		Very low		
Percutaneous nephrolitho-tomy	Venous thrombo-embolism	Low-risk	2.0	-3.7	Very low	Weak - against	Weak – against
		Medium-risk	4.0	-2.7	Very low	Weak - against	Weak – against
		High-risk	7.0	-1.2	Very low	Weak - against	Weak - for
	Bleeding requiring reoperation		9.0		Low		

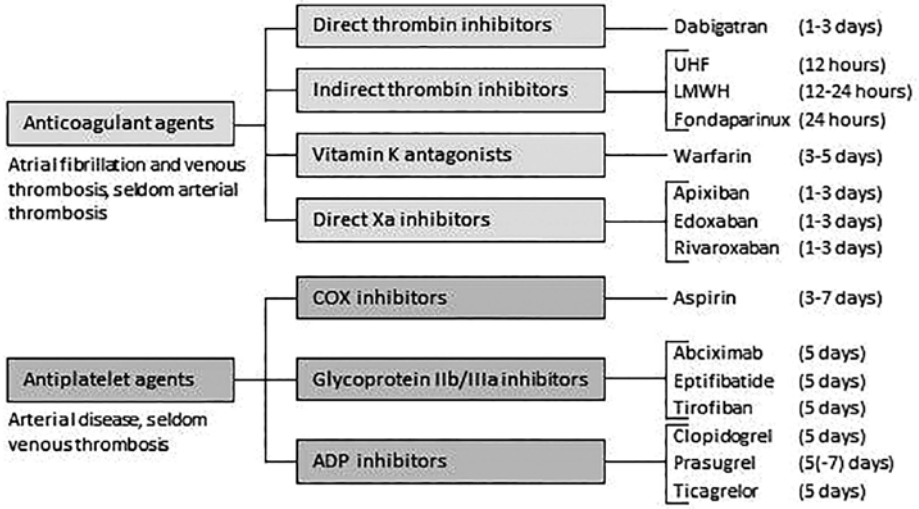
* The Panel understands that patients will receive anticoagulation in the peri-operative period. The recommendations against refer to extended prophylaxis.

3.2 Peri-operative management of antithrombotic agents in urology

*3.2.1 **Introduction***

In principle, there are four options to manage use of antithrombotic agents (Figure 2) during the peri-operative period: 1) to defer surgery until antithrombotic agents are not needed, 2) stop antithrombotic agents prior to surgery and restart some time after surgery, 3) continue through the surgical procedure, or 4) administer alternative antithrombotic agents that may still reduce the risk of thrombosis but with less risk of bleeding than agents patients are currently using ("bridging").

Figure 2: The most widely used antithrombotic agents in patients undergoing urologic surgery
Required period of stopping drug before surgery (if desired) provided in parentheses.



*3.2.2 **Evidence summary***

Earlier major guidelines addressing perioperative management of antithrombotic agents in surgery [2, 33-35] preceded recent major studies, including large, rigorous randomised trials [15, 36-38]. With respect to anti-platelet agents, a recent large, rigorous randomised trial comparing aspirin to placebo has demonstrated that aspirin increases post-operative bleeding without reducing arterial thrombotic events [15]. These results provide indirect evidence for antiplatelet agents other than aspirin. Although the absence of large, rigorous placebo-controlled trials to inform recommendations for other antiplatelet agents constitutes a limitation, given similar antithrombotic and bleeding profiles, the indirect evidence provides useful information to inform our recommendations.

Recommendations that preceded the recent much higher-quality evidence often recommended, in the peri-operative context, substitution of alternative agents for the antithrombotic agents patients were using on a regular basis [39]. The recent evidence has demonstrated that bridging increases bleeding without preventing thrombosis. The Panel therefore essentially have two recommendations for patients receiving antithrombotic agents regularly and contemplating surgery: 1) discontinue antithrombotic therapy for the period around surgery, or 2) in those with a temporary very high risk of thrombosis, delay surgery until that risk decreases. If it is not possible to delay, continuing antithrombotic therapy or bridging through surgery may be advisable.

*3.2.3 **Recommendations***

Five days is an appropriate time to stop antiplatelet agents before surgery while the optimal time to stop varies across anticoagulants (for details, see Figure 2).

R24. In all patients receiving antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor), except those with very high risk of thrombosis (see recommendations 26 and 27), the Panel recommends stopping antiplatelet agents before surgery and not initiating any alternative antithrombotic therapy (***strong, high-quality evidence***).

R25. In patients in whom antiplatelet agents have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk – typically four days post-surgery – rather than withholding for longer periods (***strong, moderate-quality evidence***).

R26. In patients with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within six weeks; transient ischemic attack (TIA) or

stroke within 30 days) in whom surgery can be delayed, the Panel recommends delaying surgery (***strong, high-quality evidence***).

R27. In patients with very high risk of thrombosis receiving antiplatelet agents (those with: drug-eluting stent placement within six months; bare metal stent placement within six weeks; TIA or stroke within 30 days) in whom surgery cannot be delayed, the Panel suggests continuing the drugs through surgery (***weak, low-quality evidence***).

R28. In all patients receiving anticoagulant agents (unfractionated heparin, low molecular weight heparin, warfarin, fondaparinux, dabigatran, apixaban, rivaroxaban, edoxaban), except those with very high risk of thrombosis (see recommendation 26), the Panel recommends stopping drugs before surgery (see Figure 2) and not initiating any alternative antithrombotic therapy (***strong, high-quality evidence***).

Note: Patients with creatinine clearance < 30 ml/min should not receive dabigatran, apixaban, rivaroxaban or edoxaban.

R29. In patients in whom anticoagulants have been stopped before surgery, the Panel recommends restarting when bleeding is no longer a serious risk – typically four days post-surgery – rather than withholding for longer periods (***strong, moderate-quality evidence***).

R30. In patients with a new VTE, it is recommended that surgery is delayed for at least one month, and if possible three months, to permit discontinuation of anticoagulation pre-operatively, rather than operating within one month of thrombosis (***strong, high-quality evidence***).

R31. In patients receiving any anticoagulant with a severe thrombophilia, such as antithrombin deficiency and antiphospholipid antibody syndrome, the Panel suggests anticoagulation with either heparin or low molecular weight heparin through surgery, rather than stopping anticoagulation before and after surgery (***weak, low-quality evidence***).

R32. In patients with high-risk mechanical prosthetic heart valves, such as cage-ball valves, receiving warfarin, the Panel recommends bridging with LMWH prior and subsequent to surgery, rather than discontinuing anticoagulation peri-operatively (***strong, high-quality evidence***).

Anticoagulation in these patients involves stopping the warfarin five days prior, commencing LMWH four days prior, omitting LMWH on the day of surgery, and recommencing LMWH and warfarin after surgery.

4. RESEARCH RECOMMENDATIONS

The evidence base for this guideline is limited. Much of the evidence regarding baseline risk is low, or very low quality [8, 9]. Prospective observational studies to establish baseline risk of VTE and bleeding in a wide variety of urologic procedures, as well as addressing patient risk factors for both thrombosis and bleeding, will be necessary to create more definite guidelines. Examples of procedures in which the evidence base is particularly limited include robotic cystectomy, laparoscopic radical nephrectomy, open nephroureterectomy, TURP and prolapse surgery. To confidently establish the baseline risk of VTE and bleeding for specific surgery will require studies that meet certain methodologic standards, such as comprehensive characterisation of the patient populations and follow-up times, documentation of the prophylaxis used, and explicit criteria with demonstration of reproducibility of judgments for documentation of DVT, PE, and bleeding assessments. Furthermore, the optimal timing and duration of thromboprophylaxis remains unclear. Timing and duration questions will be best addressed by large-scale randomised trials.

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6. CONFLICT OF INTEREST

All members of the Thromboprophylaxis working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a nonprofit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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8. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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EAU Guidelines on

Upper Urinary Tract Urothelial Carcinoma

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1. INTRODUCTION

1.1 Aim and scope

The European Association of Urology (EAU) Non-muscle-invasive Bladder Cancer (NMIBC) Guidelines Panel has compiled these clinical guidelines to provide urologists with evidence-based information and recommendations for the management of upper urinary tract urothelial carcinoma (UTUC). Separate EAU guidelines documents are available addressing non-muscle-invasive bladder cancer [1], muscle-invasive and metastatic bladder cancer (MIBC) [2], and primary urethral carcinoma [3].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The European Association of Urology (EAU) Guidelines Panel on NMIBC consists of an international multidisciplinary group of clinicians, including urologists, uro-oncologists, a radiologist, a pathologist, and a statistician. Members of this panel have been selected based on their expertise and to represent the professionals treating patients suspected of harbouring urothelial carcinoma (UC). In the course of 2021 two patient representatives have formally joined the NMIBC Panel. All involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available in print and as an app for iOS and Android devices, presenting the main findings of the UTUC Guidelines. These are abridged versions which may require consultation together with the full text version. Several scientific publications are available as are a number of translations of all versions of the EAU UTUC Guidelines, the most recent scientific summary was published in 2020 [4]. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

1.4 Publication history & summary of changes

The first EAU Guidelines on UTUC were published in 2011. This 2022 publication presents a limited update of the 2021 version.

1.4.1 Summary of changes

The literature for the complete document has been assessed and updated, whenever relevant. Conclusions and recommendations have been rephrased and added to throughout the current document.

Key changes for the 2022 print can be found in:

- Section 3.1 – Epidemiology, due to the inclusion of additional data on mismatch repair testing, Figure 3.1: Selection of patients with UTUC for Lynch syndrome screening during the first medical Interview, was revised.
- Chapter 6 – Prognosis, considerable data has been added;
- 7.1.2 Management of high-risk non-metastatic UTUC – New Section 7.1.3.2.2 Immunotherapy, was added.
- 7.2.3 Systemic treatments. This section has been completely restructured and updated, resulting in a number of changes to the Summary of changes and guidelines for the treatment of metastatic UTUC.

7.2.4 ***Summary of evidence and guidelines for the treatment of metastatic UTUC***

Summary of evidence	**LE**
Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin.	1b
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b

PD-L1 inhibitor atezolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
Erdafitinib improves OS in in platinum-refractory patients with locally advanced or metastatic UC and FGFR DNA genomic alterations (*FGFR2* or *3* mutations, or *FGFR3* fusions).	2a

Recommendation	Strength rating
First-line treatment for cisplatin-eligible patients	
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin.	Strong
First-line treatment in patients unfit for cisplatin	
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.	Strong
Second-line treatment	
Offer erdafitinib in platinum-refractory tumours with FGFR alterations.	Strong

FGFR = fibroblast growth factor receptors.

2. METHODS

2.1 Data identification

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. For the 2022 UTUC Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between May 29th 2020 and June 8th 2021. Databases searched included Pubmed, Ovid, EMBASE and both the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. After deduplication, a total of 823 unique records were identified, retrieved, and screened for relevance.

Excluded from the search were basic research studies, case series, reports, and editorial comments. Only articles published in the English language, addressing adults, were included. The publications identified were mainly retrospective, including some large multicentre studies. Owing to the scarcity of randomised data, articles were selected based on the following criteria: evolution of concepts, intermediate- and long-term clinical outcomes, study quality, and relevance. Older studies were only included if they were historically relevant. A total of 45 new publications were included in the 2022 UTUC Guidelines print. A detailed search strategy is available online: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/?type=appendicespublications.

For Chapters 3-6 (Epidemiology, Aetiology and Pathology, Staging and Classification systems, Diagnosis and Prognosis) references used in this text are assessed according to their level of evidence (LE) based on the 2009 Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence [5]. For the Disease Management and Follow-up chapters (Chapters 7 and 8) a system modified from the 2009 CEBM LEs has been used [5]. For each recommendation within the guidelines there is an accompanying online strength rating form, based on a modified GRADE methodology [6, 7]. These forms address a number of key elements, namely:

1. The overall quality of the evidence which exists for the recommendation [5];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative

management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences [8].

Additional information can be found in the general Methodology section of this print, and online at the EAU website; https://uroweb.org/guidelines/policies-and-methodological-documents/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2021 UTUC Guidelines have been peer-reviewed prior to publication.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

3.1 Epidemiology

Urothelial carcinomas are the sixth most common tumours in developed countries [9]. They can be located in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract. Bladder tumours account for 90–95% of UCs and are the most common urinary tract malignancy [1]. Upper urinary tract UCs are uncommon and account for only 5–10% of UCs [9] with an estimated annual incidence in Western countries of almost two cases per 100,000 inhabitants. This rate has risen in the past few decades as a result of improved detection and improved bladder cancer survival [10, 11]. Pyelocaliceal tumours are approximately twice as common as ureteral tumours and multifocal tumours are found in approximately 10–20% of cases [12]. The presence of concomitant carcinoma *in situ* of the upper tract is between 11% and 36% [10]. In 17% of cases, concurrent bladder cancer is present [13] whilst a prior history of bladder cancer is found in 41% of American men but in only 4% of Chinese men [14]. This, along with genetic and epigenetic factors, may explain why Asian patients present with more advanced and higher grade disease compared to other ethnic groups [10]. Following treatment, recurrence in the bladder occurs in 22–47% of UTUC patients, depending on initial tumour grade [15] compared with 2–5% in the contralateral upper tract [16].

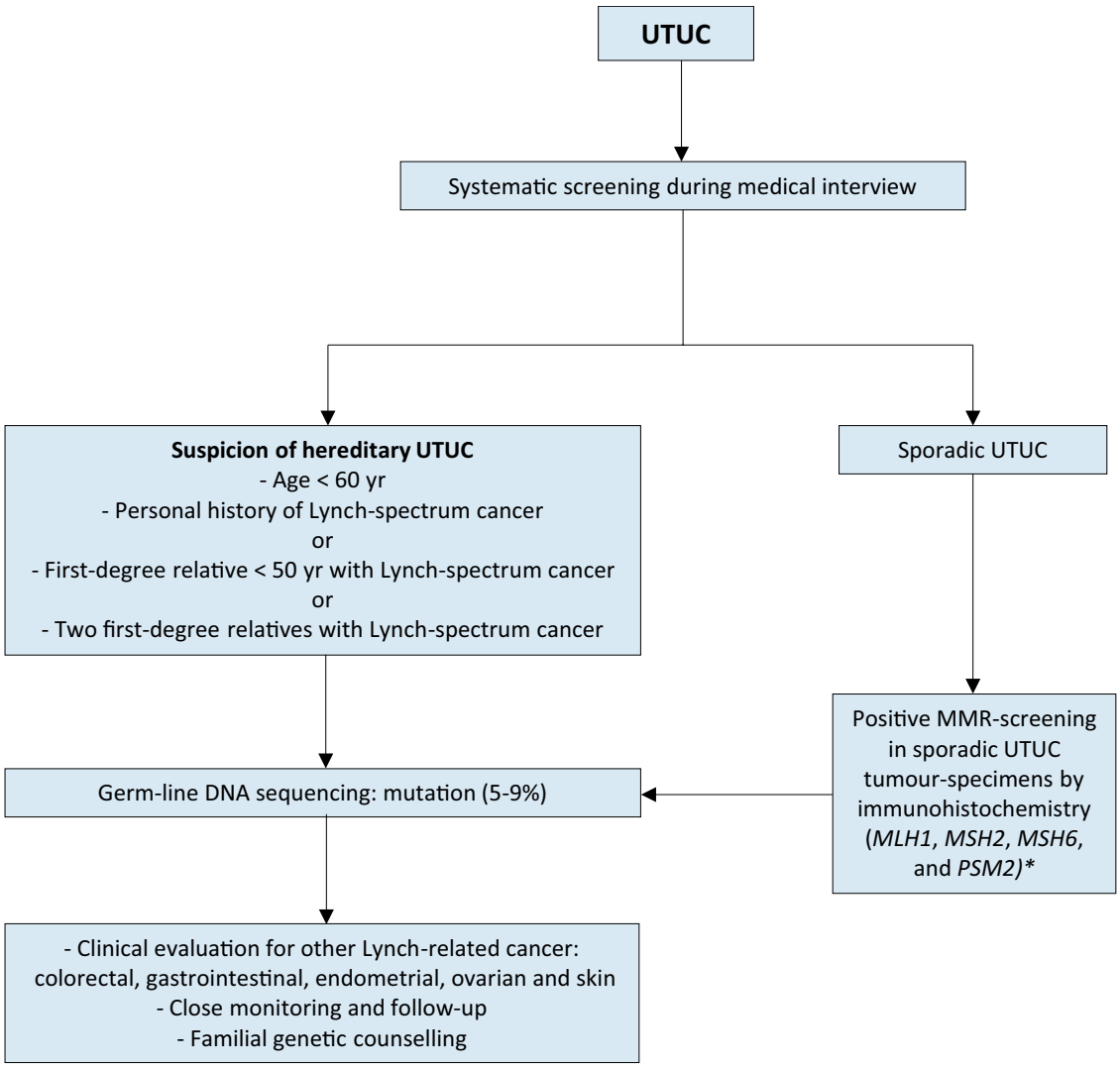
With regards to UTUC occurring following an initial diagnosis of bladder cancer, a series of 82 patients treated with bacillus Calmette-Guérin (BCG) who had regular upper tract imaging between years 1 and 3 showed a 13% incidence of UTUC, all of which were asymptomatic [17], whilst in another series of 307 patients without routine upper tract imaging the incidence was 25% [18]. A multicentre cohort study (n = 402) with a 50 month follow-up has demonstrated a UTUC incidence of 7.5% in NMIBC receiving BCG with predictors being intravesical recurrence and non-papillary tumour at transurethral resection of the bladder [19]. Following radical cystectomy for MIBC, 3–5% of patients develop a metachronous UTUC [20, 21].

Approximately two-thirds of patients who present with UTUCs have invasive disease at diagnosis compared to 15–25% of patients presenting with muscle-invasive bladder tumours [22]. This is probably due to the absence of muscularis propria layer in the upper tract, so tumours are more likely to upstage at an earlier time-point. Approximately 9% of patients present with metastasis [10, 23, 24]. Upper urinary tract UCs have a peak incidence in individuals aged 70–90 years and are twice as common in men [25].

Upper tract UC and bladder cancer exhibit significant differences in the prevalence of common genomic alterations. In individual patients with a history of both tumours, bladder cancer and UTUC were always clonally related. Genomic characterisation of UTUC provides information regarding the risk of bladder recurrence and can identify tumours associated with Lynch syndrome [26].

The Amsterdam criteria are a set of diagnostic criteria used by doctors to help identify families which are likely to have Lynch syndrome [27]. In Lynch-related UTUC, immunohistochemistry (IHC) analysis showed loss of protein expression corresponding to the disease-predisposing MMR (mismatch repair) gene mutation in 98% of the samples (46% were microsatellite instable and 54% microsatellite stable) [28]. The majority of tumours develop in *MSH2* mutation carriers [28]. Patients identified at high risk for Lynch syndrome should undergo DNA sequencing for patient and family counselling [29, 30]. Germline mutations in DNA MMR genes defining Lynch syndrome, are found in 9% of patients with UTUC compared to 1% of patients with bladder cancer, linking UTUC to Lynch syndrome [31]. A study of 115 consecutive UTUC patients, reported that 13.9% screened positive for potential Lynch syndrome and 5.2% had confirmed Lynch syndrome [32]. This is one of the highest rates of undiagnosed genetic disease in urological cancers, which justifies screening of all patients under 60 presenting with UTUC and those with a family history of UTUC (see Figure 3.1) [33, 34] or positive reflexive MMR-test by IHC in sporadic UTUC [31, 35-37].

Figure 3.1: Selection of patients with UTUC for Lynch syndrome screening during the first medical interview


UTUC
Systematic screening during medical interview
Suspicion of hereditary UTUC
- Age < 60 yr
- Personal history of Lynch-spectrum cancer
or
- First-degree relative < 50 yr with Lynch-spectrum cancer
or
- Two first-degree relatives with Lynch-spectrum cancer
Sporadic UTUC
Positive MMR-screening in sporadic UTUC tumour-specimens by immunohistochemistry (MLH1, MSH2, MSH6, and PSM2)*
Germ-line DNA sequencing: mutation (5-9%)
- Clinical evaluation for other Lynch-related cancer: colorectal, gastrointestinal, endometrial, ovarian and skin
- Close monitoring and follow-up
- Familial genetic counselling

**Sporadic UTUC that for any reason has undergone MMR screening with a positive result should test for germ-line DNA sequencing mutations.*

MMR = mismatch repair; mismatch repair genes = MLH1, MSH2, MSH6, and PSM2; UTUC = upper urinary tract urothelial carcinoma.

3.2 Risk factors

A number of environmental factors have been implicated in the development of UTUC [12, 38]. Published evidence in support of a causative role for these factors is not strong, with the exception of smoking and aristolochic acid. Tobacco exposure increases the relative risk of developing UTUC from 2.5 to 7.0 [39-41]. A large population-based study assessing familial clustering in relatives of UC patients, including 229,251 relatives of case subjects and 1,197,552 relatives of matched control subjects, has demonstrated genetic or environmental roots independent of smoking-related behaviours. With more than 9% of the cohort being UTUC patients, clustering was not seen in upper tract disease. This may suggest that the familial clustering of UC is specific to lower tract cancers [42].

In Taiwan and Chile, the presence of arsenic in drinking water has been tentatively linked to UTUC [43, 44]. Aristolochic acid, a nitrophenanthrene carboxylic acid produced by Aristolochia plants, which are used worldwide, especially in China and Taiwan [45], exerts multiple effects on the urinary system. Aristolochic acid irreversibly injures renal proximal tubules resulting in chronic tubulointerstitial disease, while the mutagenic properties of this chemical carcinogen lead predominantly to UTUC [45-47]. Aristolochic acid has been linked to bladder cancer, renal cell carcinoma, hepatocellular carcinoma, and intrahepatic cholangiocarcinoma [48]. Two routes of exposure to aristolochic acid are known: (i) environmental contamination of agricultural products by Aristolochia plants, as reported for Balkan endemic nephropathy [49]; and (ii) ingestion of Aristolochia-

based herbal remedies [50, 51]. Following bioactivation, aristolochic acid reacts with genomic DNA to form aristolactam-deoxyadenosine adducts [52]; these lesions persist for decades in target tissues, serving as robust biomarkers of exposure [9]. These adducts generate a unique mutational spectrum, characterised by A>T transversions located predominately on the non-transcribed strand of DNA [48, 53]. However, fewer than 10% of individuals exposed to aristolochic acid develop UTUC [47].

Two retrospective series found that aristolochic acid-associated UTUC is more common in females [54, 55]. However, females with aristolochic acid UTUC have a better prognosis than their male counterparts. Consumption of arsenic in drinking water and aristolochia-based herbal remedies together appears to have an additive carcinogenic effect [56].

Alcohol consumption is associated with development of UTUC. A large case-control study (1,569 cases and 506,797 controls) has evidenced a significantly higher risk of UTUC in ever-drinkers compared to never-drinkers (OR: 1.23; 95% CI: 1.08–1.40, p = 0.001). Compared to never-drinkers, the risk threshold for UTUC was > 15 g of alcohol/day. A dose-response was observed [57].

Differences in the ability to counteract carcinogens may contribute to host susceptibility to UTUC. Some genetic polymorphisms are associated with an increased risk of cancer or faster disease progression that introduces variability in the inter-individual susceptibility to the risk factors previously mentioned. Upper urinary tract UCs may share some risk factors and described molecular pathways with bladder UC [26]. So far, two UTUC-specific polymorphisms have been reported [58].

A history of bladder cancer is associated with a higher risk of developing UTUCs (see Section 3.1). Patients who undergo ureteral stenting at the time of TURB, including prior to radical cystectomy are at higher risk for upper tract recurrence [59, 60].

3.3 Histology and classification

3.3.1 ***Histological types***

Upper urinary tract tumours are almost always UCs and pure non-urothelial histology is rare [53, 54]. However, variants are present in approximately 25% of UTUCs [55, 56]. Pure squamous cell carcinoma of the urinary tract is often assumed to be associated with chronic inflammatory diseases and infections arising from urolithiasis [57, 58]. Urothelial carcinoma with divergent squamous differentiation is present in approximately 15% of cases [57]. Keratinising squamous metaplasia of urothelium is a risk factor for squamous cell cancers and therefore mandates surveillance. Upper urinary tract UCs with variant histology are high-grade and have a worse prognosis compared with pure UC [56, 59, 60]. Other variants, although rare, include sarcomatoid and UCs with inverted growth [60].

However, collecting duct carcinomas, which may seem to share similar characteristics with UCs, display a unique transcriptomic signature similar to renal cancer, with a putative cell of origin in the distal convoluted tubules. Therefore, collecting duct carcinomas are considered as renal tumours [61].

3.4 Summary of evidence and recommendations for epidemiology, aetiology, and pathology

Summary of evidence	LE
Aristolochic acid and smoking exposure increase the risk for UTUC.	2a
Patients with Lynch syndrome are at risk for UTUC.	2a

Recommendations	Strength rating
Evaluate patient and family history based on the Amsterdam criteria to identify patients with upper tract urothelial carcinoma.	Weak
Evaluate patient exposure to smoking and aristolochic acid.	Weak

4. STAGING AND CLASSIFICATION SYSTEMS

4.1 Classification

The classification and morphology of UTUC and bladder carcinoma are similar [1]. However because of the difficulty in adequate sample acquisition, it is often difficult to distinguish between non-invasive papillary tumours [70], flat lesions (carcinoma *in situ* [CIS]), and invasive carcinoma. Therefore, histological grade is often used for clinical decision making as it is strongly associated with pathological stage [71].

4.2 Tumour Node Metastasis staging

The tumour, node, metastasis (TNM) classification is shown in Table 1 [72]. The regional lymph nodes (LNs) are the hilar and retroperitoneal nodes and, for the mid- and distal ureter, the pelvic nodes. Laterality does not affect N classification.

4.3 Tumour grade

In 2004, the WHO and the International Society of Urological Pathology published a new histological classification of UCs which provides a different patient stratification between individual categories compared to the older 1973 WHO classification [73, 74]. In 2016, an update of the 2004 WHO grading classification was published without major changes [73]. These guidelines are still based on both the 1973 and 2004/2016 WHO classifications since most published data use the 1973 classification [70].

Table 1: TNM classification 2017 for upper tract urothelial cell carcinoma [72]

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

TNM = Tumour, Node, Metastasis (classification).

4.4 Molecular classification of UTUCs

A number of studies focussing on molecular classification have been able to demonstrate genetically distinct groups of UTUC by evaluating DNA, RNA and protein expression. Five molecular subtypes with different gene expression, tumour location and outcome have been identified, but, as yet, it is unclear whether these subtypes will respond differently to treatment [75].

5. DIAGNOSIS

5.1 Symptoms

The diagnosis of UTUC may be incidental or symptom related. The most common symptom is visible or nonvisible haematuria (70–80%) [76, 77]. Flank pain, due to clot or tumour tissue obstruction or less often due to local growth, occurs in approximately 20–32% of cases [78]. Systemic symptoms (including anorexia, weight loss, malaise, fatigue, fever, night sweats, or cough) associated with UTUC should prompt evaluation for metastases associated with a worse prognosis [78].

5.2 Imaging

5.2.1 ***Computed tomography urography***

Computed tomography (CT) urography has the highest diagnostic accuracy of the available imaging techniques [79]. A meta-analysis of 13 studies comprising 1,233 patients revealed a pooled sensitivity of CT urography for UTUC of 92% (CI: 0.85–0.96) and a pooled specificity of 95% (CI: 0.88–0.98) [80].

Rapid acquisition of thin sections allows high-resolution isotropic images that can be viewed in multiple planes to assist with diagnosis without loss of resolution. Epithelial "flat lesions" without mass effect or urothelial thickening are generally not visible with CT.

The presence of enlarged LNs is highly predictive of metastases in UTUC [81, 82].

5.2.2 ***Magnetic resonance urography***

Magnetic resonance (MR) urography is indicated in patients who cannot undergo CT urography, usually when radiation or iodinated contrast media are contraindicated [83]. The sensitivity of MR urography is 75% after contrast injection for tumours < 2 cm [83]. The use of MR urography with gadolinium-based contrast media should be limited in patients with severe renal impairment (< 30 mL/min creatinine clearance), due to the risk of nephrogenic systemic fibrosis. Computed tomography urography is more sensitive and specific for the diagnosis and staging of UTUC compared to MR urography [84].

5.3 Cystoscopy

Urethrocystoscopy is an integral part of UTUC diagnosis to rule out concomitant bladder cancer [10, 13].

5.4 Cytology

Abnormal cytology may indicate high-grade UTUC when bladder cystoscopy is normal, and in the absence of CIS in the bladder and prostatic urethra [1, 85, 86]. Cytology is less sensitive for UTUC than bladder tumours and should be performed selectively for the affected upper tract [87]. In a recent study, barbotage cytology detected up to 91% of cancers [88]. Barbotage cytology taken from the renal cavities and ureteral lumina is preferred before application of a contrast agent for retrograde ureteropyelography as it may cause deterioration of cytological specimens [89]. Retrograde ureteropyelography remains an option to detect UTUCs [79, 90, 91].

The sensitivity of fluorescence *in situ* hybridisation (FISH) for molecular abnormalities characteristic of UTUCs is approximately 50% and therefore its use in clinical practice remains unproven [92, 93].

5.5 Diagnostic ureteroscopy

Flexible ureteroscopy (URS) is used to visualise the ureter, renal pelvis and collecting system and for biopsy of suspicious lesions. Presence, appearance and size of tumour can be determined using URS. In addition, ureteroscopic biopsies can determine tumour grade in more than 90% of cases with a low false-negative rate, regardless of sample size [94]. Undergrading may occur following diagnostic biopsy, making intensive follow-up necessary if kidney-sparing treatment is chosen [71, 95]. Ureteroscopy also facilitates selective ureteral sampling for cytology *in situ* [91, 96, 97]. Stage assessment using ureteroscopic biopsy is inaccurate. Combining ureteroscopic biopsy grade, imaging findings such as hydronephrosis, and urinary cytology may help in the decision-making process between radical nephroureterectomy (RNU) and kidney-sparing therapy [97, 98]. In a meta-analysis comparing URS vs. no URS prior to RNU, 8/12 studies found an increased risk for intravesical recurrence if URS was performed before RNU [99]. Performing a biopsy at URS was also identified as a risk factor for intravesical recurrence [99].

Technical developments in flexible ureteroscopes and the use of novel imaging techniques improve visualisation and diagnosis of flat lesions [100]. Narrow-band imaging is a promising technique, but results are preliminary [101]. Optical coherence tomography and confocal laser endomicroscopy (Cellvizio®) have been used *in vivo* to evaluate tumour grade and/or for staging purposes, with a promising correlation with definitive histology in high-grade UTUC [102, 103]. Recommendations for the diagnosis of UTUC are listed in Section 5.7.

5.6 Distant metastases

Prior to any treatment with curative intent, it is essential to rule out distant metastases. Computed tomography is the diagnostic technique of choice for lung- and abdominal staging for metastases [80]. A SEER analysis shows that approximately 9% of patients present with distant metastases [104].

5.6.1 ***^{18}F-Fluorodeoxglucose positron emission tomography/computed tomography***

A retrospective multi-centre publication on the use of ^{18}F-Fluorodeoxglucose positron emission tomography/computed tomography (FDG-PET/CT) for the detection of nodal metastasis in 117 surgically-treated UTUC patients reported a promising sensitivity and specificity of 82% and 84%, respectively. Suspicious LNs on FDG-PET/CT were associated with worse recurrence-free survival [105]. These results warrant further validation and comparison with MR urography and CT.

5.7 Summary of evidence and guidelines for the diagnosis of UTUC

Summary of evidence	LE
The diagnosis and staging of UTUC is best done with computed tomography urography and URS.	2a
Selective urinary cytology has high sensitivity in high-grade tumours, including carcinoma *in situ*.	3
Urethrocystoscopy can detect concomitant bladder cancer.	2a

Recommendations	Strength rating
Perform a urethrocystoscopy to rule out bladder tumour.	Strong
Perform a computed tomography (CT) urography for diagnosis and staging.	Strong
Use diagnostic ureteroscopy and biopsy if imaging and cytology are not sufficient for the diagnosis and/or risk-stratification of the tumour.	Strong
Magnetic resonance urography or ^{18}F-Fluorodeoxglucose positron emission tomography/CT may be used when CT is contra-indicated.	Weak

6. PROGNOSIS

6.1 Prognostic factors

Many prognostic factors have been identified and can be used to risk-stratify patients in order to decide on the most appropriate local treatment (radical vs. conservative) and discuss peri-operative systemic therapy. Factors can be divided into patient-related factors and tumour-related factors.

*6.1.1 **Patient-related factors***

6.1.1.1 Age and gender

Older age at the time of RNU is independently associated with decreased cancer-specific survival (CSS) [106, 107] (LE: 3). Gender has no impact on prognosis of UTUC [108].

6.1.1.2 Ethnicity

One multicentre study in academic centres did not show any difference in outcomes between races [109], but U.S. population-based studies have indicated that African-American patients have worse outcomes than other ethnicities (LE: 3). Whether this is related to access to care or biological and/or patterns of care remains unknown. Another study has demonstrated differences between Chinese and American patients at presentation (risk factor, disease characteristics and predictors of adverse oncologic outcomes) [14].

6.1.1.3 Tobacco consumption

Being a smoker at diagnosis increases the risk for disease recurrence, mortality [110, 111] and intravesical recurrence after RNU [112] (LE: 3). There is a close relationship between tobacco consumption and prognosis [113] (LE: 3); smoking cessation improves cancer control [111].

6.1.1.4 Surgical delay

A delay between diagnosis of an invasive tumour and its removal may increase the risk of disease progression. Once a decision regarding RNU has been made, the procedure should be carried out within twelve weeks, when possible [114-118] (LE: 3).

6.1.1.5 Other factors

Comorbidity and performance indices (e.g. American Society of Anesthesiologists [ASA], performance status [PS], and Charlson Comorbidity Index) are also associated with worse survival outcomes across disease stages [119-122].

A higher ASA score confers worse CSS after RNU [123] (LE: 3), as does poor PS [124]. Obesity and higher body mass index adversely affect cancer-specific outcomes in patients treated with RNU [125] (LE: 3), with potential differences between races [126]. Several blood-based biomarkers have been associated with locally advanced disease and cancer-specific mortality such as high pre-treatment-derived neutrophil-lymphocyte ratio [127-130], low albumin [129, 131], high C-reactive protein [129] or modified Glasgow score [132], high De Ritis ratio (aspartate transaminase/alanine transaminase) [133], altered renal function [129, 134] and high fibrinogen [129, 134] (LE: 3).

6.1.2 *Tumour-related factors*

6.1.2.1 *Tumour stage and grade*

The main prognostic factors are tumour stage and grade [22, 97, 107, 135]. Upper urinary tract UCs that invade the muscle wall have a poor prognosis. In a large Dutch series of UTUC, 5-year CSS was 86% for non-muscle-invasive tumours, 70% for muscle-invasive organ-confined tumours and 44% for locally-advanced tumours [136]. A SEER contemporary analysis of RNUs for high-risk disease showed that 5-year CSS was 86% for T1N0, 77% for T2N0, 63% for T3N0 and 39% for T4N0/T any N1-3 [137].

6.1.2.2 *Tumour location, multifocality, size and hydronephrosis*

Initial location of the UTUC is a prognostic factor in some studies [138, 139] (LE: 3). After adjustment for the effect of tumour stage, patients with ureteral and/or multifocal tumours seem to have a worse prognosis than patients diagnosed with renal pelvic tumours [140-145]. Hydronephrosis is associated with advanced disease and poor oncological outcome [81, 89, 146]. Increasing tumour size is associated with a higher risk of muscle-invasive and/or non-organ-confined disease, both in ureteral and renal pelvis UTUC. A large multi-institutional retrospective study including 932 RNUs performed for non-metastatic UTUC demonstrated that 2 cm appears to be the best cut-off in identifying patients at risk of harbouring ≥ pT2 UTUC [147]. In a SEER database analysis of 4,657 patients with renal pelvis UTUC, each gain of 1 cm in tumour size was associated with a 1.25-fold higher risk of pT2–T4 histology at RNU [104].

6.1.2.3 *Variant histology*

Pathological variants are associated with worse cancer-specific and overall survival (OS) [64] (LE: 3). Most studied variants are micropapillary [67], squamous [148] and sarcomatoid [67] which are consistently associated with locally-advanced disease and worse outcome.

6.1.2.4 *Lymph node involvement*

Patients with nodal metastasis experience very poor survival after surgery [149]. Lymph node density (cut-off 30%) and extranodal extension are powerful predictors of survival outcomes in N+ UTUC [150-152]. Lymph node dissection (LND) performed at the time of RNU allows for optimal tumour staging, although its curative role remains controversial [151, 153-155] (LE: 3).

6.1.2.5 *Lymphovascular invasion*

Lymphovascular invasion (LVI) is present in approximately 20% of invasive UTUCs and is an independent predictor of survival [156-158]. Lymphovascular invasion status should be specifically reported in the pathological reports of all UTUC specimens [156, 159, 160] (LE: 3).

6.1.2.6 *Surgical margins*

Positive soft tissue surgical margin is associated with a higher disease recurrence after RNU. Pathologists should look for and report positive margins at the level of ureteral transection, bladder cuff, and around the tumour [161] (LE: 3).

6.1.2.7 *Other pathological factors*

Extensive tumour necrosis (> 10% of the tumour area) is an independent prognostic predictor in patients who undergo RNU [162, 163] (LE: 3). In case neoadjuvant treatment was administered, pathological downstaging is associated with better OS [164, 165] (LE: 3). The architecture of UTUC, as determined from pathological examination of RNU specimens, is also a strong prognosticator with sessile growth pattern being associated with worse outcome [166-168] (LE: 3). Concomitant CIS in organ-confined UTUC and a history of bladder CIS are associated with a higher risk of recurrence and cancer-specific mortality [169, 170] (LE: 3). Macroscopic infiltration or invasion of peri-pelvic adipose tissue confers a higher risk of disease recurrence after RNU compared to microscopic infiltration of renal parenchyma [63, 171].

6.1.3 ***Molecular markers***

Because of the rarity of UTUC, the main limitations of molecular studies are their retrospective design and, for most studies, small sample size. None of the investigated markers have been validated yet to support their introduction in daily clinical decision making [140, 172].

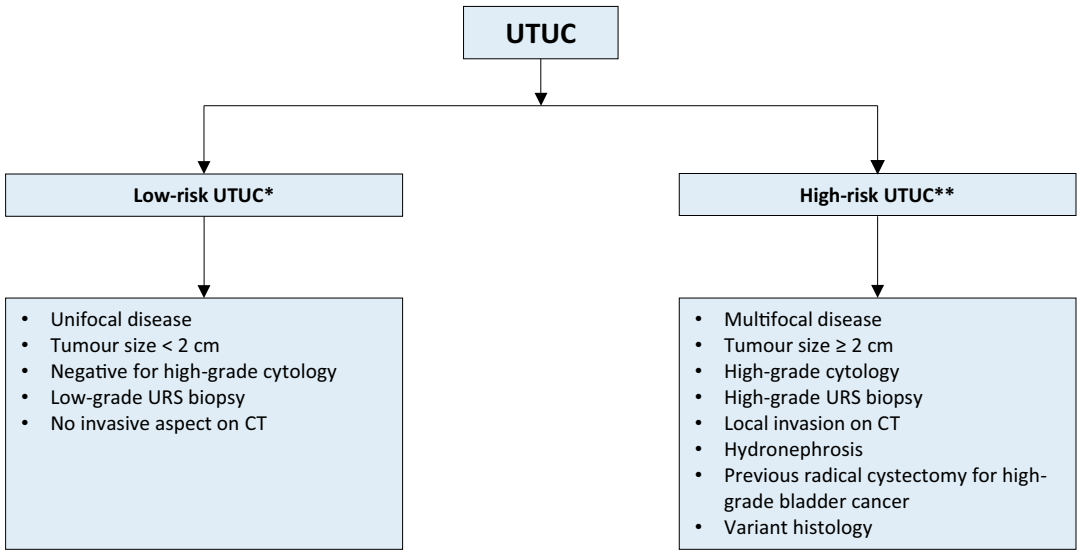
6.2 Risk stratification for clinical decision making

6.2.1 ***Low- versus high-risk UTUC***

As tumour stage is difficult to assess clinically in UTUC, it is useful to “risk stratify” UTUC between low- and high risk of progression to identify those patients who are more likely to benefit from kidney-sparing treatment and those who should be treated radically [173, 174] (see Figure 6.2). The factors to consider for risk stratification are presented in Figure 6.1.

Several new risk stratification models have been assessed to improve upon the dichotomous EAU risk grouping, with the main aim to avoid overtreatment (i.e., better stratify patients eligible for kidney-sparing surgery). Examples include multivariable models with novel clinical characteristics [175] a tumour grade-and stage-based model [176] and a three-tier risk stratification model (i.e., low-, intermediate-, and high risk) [177]. These models need further validation.

Figure 6.1: Risk stratification of non-metastatic UTUC

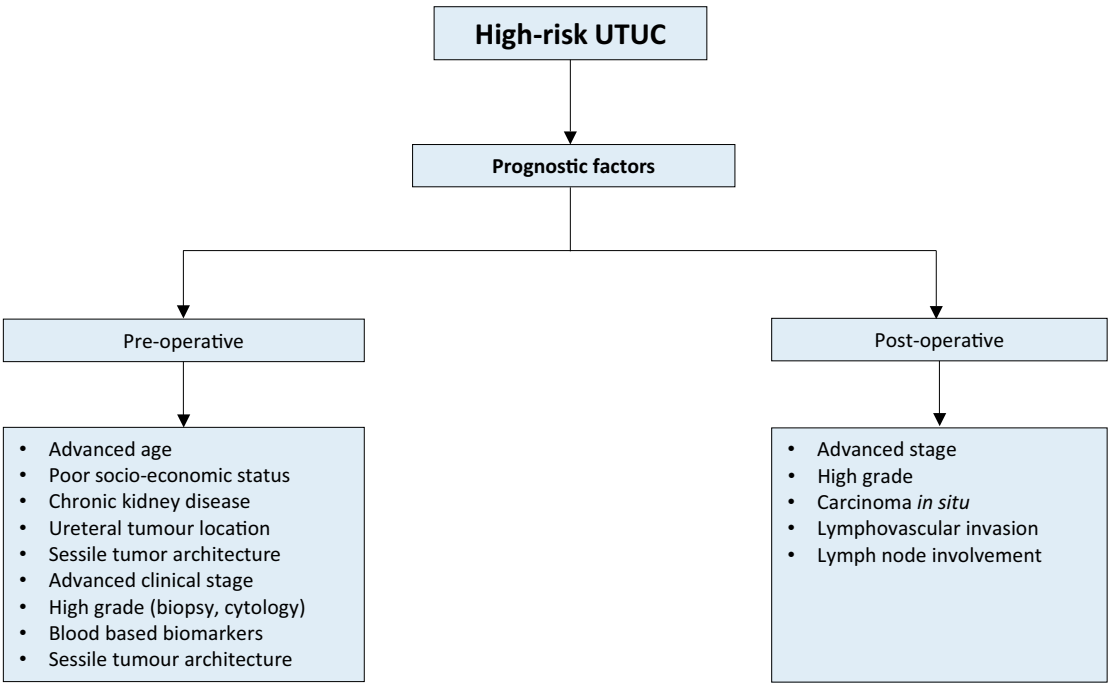


CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.
** All these factors need to be present.*
***Any of these factors need to be present.*

6.2.2 Peri-operative predictive tools for high-risk disease

There are several pre-RNU models aiming at predicting which patient has muscle-invasive/non-organ-confined disease [162, 178-181] (LE: 3). Prognostic nomograms based on pre-operative factors and post-operative pathological characteristics are available [153, 180, 182-187]. The main factors included in these models, which may be used when counselling patients regarding follow-up and administration of peri-operative chemotherapy, are detailed in Figure 6.2.

Figure 6.2: UTUC prognostic factors included in prognostic models



UTUC = upper tract urothelial carcinoma.

6.3 Bladder recurrence

A meta-analysis of available data has identified significant predictors of bladder recurrence after RNU [188] (LE: 3). Three categories of predictors for increased risk of bladder recurrence were identified:

1. Patient-specific factors such as male gender, previous bladder cancer, smoking and pre-operative chronic kidney disease.
2. Tumour-specific factors such as positive pre-operative urinary cytology, tumour grade, ureteral location, multifocality, tumour diameter, invasive pT stage, and necrosis [189].
3. Treatment-specific factors such as laparoscopic approach, extravesical bladder cuff removal, and positive surgical margins [188].

In addition, the use of diagnostic URS has been associated with a higher risk of developing bladder recurrence after RNU [190, 191] (LE: 3). Based on low-level evidence only, a single dose of intravesical chemotherapy after diagnostic/therapeutic ureteroscopy of non-metastatic UTUC has been suggested to lower the rate of intravesical recurrence, similarly to that after RNU [188].

6.4 Summary of evidence and guidelines for the prognosis of UTUC

Summary of evidence	LE
Important prognostic factors for risk stratification include tumour multifocality, size, stage, grade, hydronephrosis and variant histology.	3
Models are available to predict non-organ-confined disease and altered prognosis after RNU.	3
Patient, tumour, and treatment-related factors impact the risk of bladder recurrence.	3
Currently, no prognostic biomarkers are validated for clinical use.	3

Recommendation	Strength rating
Use prognostic factors to risk-stratify patients for therapeutic guidance.	Weak

7. DISEASE MANAGEMENT

7.1 Localised non-metastatic disease

*7.1.1 **Kidney-sparing surgery***

Kidney-sparing surgery for low-risk UTUC reduces the morbidity associated with radical surgery (e.g., loss of kidney function), without compromising oncological outcomes [192]. In low-risk cancers, it is the preferred approach as survival is similar to that after RNU [192]. This option should therefore be discussed in all low-risk cases, irrespective of the status of the contralateral kidney. In addition, it can also be considered in selected high-risk patients with a serious renal insufficiency or having a solitary kidney (LE: 3). Recommendations for kidney-sparing management of UTUC are listed in Section 7.1.1.5.

7.1.1.1 Ureteroscopy

Endoscopic ablation should be considered in patients with clinically low-risk cancer [193, 194]. A flexible ureteroscope is useful in the management of pelvicalyceal tumours [195]. The patient should be informed of the need and be willing to comply with an early second-look URS [196] and stringent surveillance; complete tumour resection or destruction is necessary [196]. Nevertheless, a risk of disease progression remains with endoscopic management due to the suboptimal performance of imaging and biopsy for risk stratification and tumour biology [197].

7.1.1.2 Percutaneous access

Percutaneous management can be considered for low-risk UTUC in the renal pelvis [193, 198] (LE: 3). This may also be offered for low-risk tumours in the lower caliceal system that are inaccessible or difficult to manage by flexible URS. However, this approach is being used less due to the availability of improved endoscopic tools such as distal-tip deflection of recent ureteroscopes [194, 198]. Moreover, a risk of tumour seeding remains with a percutaneous access [198].

7.1.1.3 Ureteral resection

Segmental ureteral resection with wide margins provides adequate pathological specimens for staging and grading while preserving the ipsilateral kidney. Lymphadenectomy can also be performed during segmental ureteral resection [192]. Segmental resection of the proximal two-thirds of ureter is associated with higher failure rates than for the distal ureter [199, 200] (LE: 3).

Distal ureterectomy with ureteroneocystostomy are indicated for low-risk tumours in the distal ureter that cannot be removed completely endoscopically and for high-risk tumours when kidney-sparing surgery for renal function preservation is desired (in case of an imperative indication) [183, 199, 201] (LE: 3). A total ureterectomy with an ileal-ureteral substitution is technically feasible, but only in selected cases when a renal-sparing procedure is mandatory and the tumour is low risk [202].

7.1.1.4 Upper urinary tract instillation of topical agents

The antegrade instillation of BCG or mitomycin C in the upper urinary tract via percutaneous nephrostomy after complete tumour eradication has been studied for CIS after kidney-sparing management [170, 203] (LE: 3). Retrograde instillation through a single J open-ended ureteric stent is also used. Both the antegrade and retrograde approach can be dangerous due to possible ureteric obstruction and consecutive pyelovenous influx during instillation/perfusion. The reflux obtained from a double-J stent has been used but this approach is suboptimal because the drug often does not reach the renal pelvis [204-207].

A systematic review and meta-analysis assessing the oncologic outcomes of patients with papillary UTUC or CIS of the upper tract treated with kidney-sparing surgery and adjuvant endocavitary treatment analysed the effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after kidney-sparing surgery for papillary non-invasive (Ta-T1) UTUCs and of adjuvant BCG for the treatment of upper tract CIS, finding no difference between the method of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS. Furthermore, the recurrence rates following adjuvant instillations are comparable to those reported in the literature in untreated patients, questioning their efficacy [208]. The analyses were based on retrospective small studies suffering from publication and reporting bias.

Recent evidence suggests that early single adjuvant intracavitary instillation of mitomycin C in patients with low-grade UTUC might reduce the risk of local recurrence [209] (LE: 3). This needs to be confirmed in further studies. The authors report limited complications related to the instillations, but propose a retrograde pyelography before instillations are commenced to exclude contrast extravasation. This concept will need further evaluation in a randomised context [209].

A single-arm phase III trial showed that the use of mitomycin-containing reverse thermal gel (UGN-101) instillations in a chemoablation setting via retrograde catheter to the renal pelvis and calyces was associated with a complete response rate in a total of 42 patients (59%) with biopsy-proven low-grade UTUC measuring less than 15 mm. The most frequently reported all-cause adverse events were ureteric stenosis in 31 (44%) of 71 patients, urinary tract infection in 23 (32%), haematuria in 22 (31%), flank pain in 21 (30%), and nausea in 17 (24%). A total of 19 (27%) of 71 patients had drug-related or procedure-related serious adverse events. No deaths were regarded as related to treatment [210].

7.1.1.5 Guidelines for kidney-sparing management of UTUC

Recommendations	Strength rating
Offer kidney-sparing management as primary treatment option to patients with low-risk tumours.	Strong
Offer kidney-sparing management (distal ureterectomy) to patients with high-risk tumours limited to the distal ureter.	Weak
Offer kidney-sparing management to patients with solitary kidney and/or impaired renal function, providing that it will not compromise survival. This decision will have to be made on a case-by-case basis in consultation with the patient.	Strong

*7.1.2 **Management of high-risk non-metastatic UTUC***

7.1.2.1 Surgical approach

7.1.2.1.1 Open radical nephroureterectomy

Open RNU with bladder cuff excision is the standard treatment of high-risk UTUC, regardless of tumour location [22] (LE: 3). Radical nephroureterectomy must be performed according to oncological principles preventing tumour seeding [22]. Section 7.1.6 lists the recommendations for RNU.

7.1.2.1.2 Minimal invasive radical nephroureterectomy

Retroperitoneal metastatic dissemination and metastasis along the trocar pathway following manipulation of large tumours in a pneumoperitoneal environment have been reported in few cases [211, 212]. Several precautions may lower the risk of tumour spillage:

1. avoid entering the urinary tract;
2. avoid direct contact between instruments and the tumour;
3. perform the procedure in a closed system. Avoid morcellation of the tumour and use an endobag for tumour extraction;
4. the kidney and ureter must be removed *en bloc* with the bladder cuff;
5. invasive or large (T3/T4 and/or N+/M+) tumours are contraindications for minimal-invasive RNU as the outcome is worse compared to an open approach [213, 214].

Laparoscopic RNU is safe in experienced hands when adhering to strict oncological principles. There is a tendency towards equivalent oncological outcomes after laparoscopic or open RNU [212, 215-218] (LE: 3). One prospective randomised study has shown that laparoscopic RNU is inferior to open RNU for non-organ-confined UTUC. However, this was a small trial (n = 80), which was likely underpowered [214] (LE: 2). Oncological outcomes after RNU have not changed significantly over the past three decades despite staging and surgical refinements [219] (LE: 3). In a population-based data set, a hospital volume of ≥ 6 patients per year treated with RNU showed improvement of short-term outcomes (30- and 90-day mortality) and overall long-term survival [220]. A robot-assisted laparoscopic approach can be considered with recent data suggesting oncologic equivalence with the other approaches [221-223].

7.1.2.1.3 Management of bladder cuff

Resection of the distal ureter and its orifice is performed because there is a considerable risk of tumour recurrence in this area and in the bladder [188, 199, 224-226]. Several techniques have been considered to simplify distal ureter resection, including the pluck technique, stripping, transurethral resection of the intramural ureter, and intussusception. None of these techniques has convincingly been shown to be equal to complete bladder cuff excision [16, 224, 225] (LE: 3).

7.1.2.1.4 Lymph node dissection

The use of a LND template is likely to have a greater impact on patient survival than the number of removed LNs [227]. Template-based and completeness of LND improves CSS in patients with muscle-invasive disease and reduces the risk of local recurrence [228]. Even in clinically [229] and pathologically [230] node-negative patients, LND improves survival. The risk of LN metastasis increases with advancing tumour stage [154]. Lymph node dissection appears to be unnecessary in cases of TaT1 UTUC because of the low risk of LN metastasis [231-234], however, tumour staging is inaccurate pre-operatively; therefore a template-based LND should be offered to all patients who are scheduled for RNU for high-risk non-metastatic UTUC. The templates for LND have been described [228, 235, 236].

*7.1.3 **Peri-operative chemotherapy***

7.1.3.1 Neoadjuvant chemotherapy

In patients treated prior to losing their renal reserve several retrospective studies evaluating the role of neoadjuvant chemotherapy have shown promising pathological downstaging and complete response rates [164, 237-240]. No RCTs have been published yet but prospective data from a phase II trial showed that the use of neoadjuvant chemotherapy was associated with a 14% pathological complete response rate for high-grade UTUC [241]. In addition, final pathological stage was ≤ ypT1 in more than 60% of included patients with acceptable toxicity profile. In a systematic review and meta-analysis comprising more than 800 patients, neoadjuvant chemotherapy has shown a pathologic partial response of 43% and a downstaging in 33% of patients, and also an OS and CSS survival benefit compared with RNU alone [242]. Furthermore, neoadjuvant chemotherapy has been shown to result in lower disease recurrence and mortality rates compared to RNU alone without compromising the use of definitive surgical treatment [239, 243-245].

7.1.3.2 Adjuvant chemotherapy

7.1.3.2.1 Chemotherapy

A phase III prospective randomised trial (n = 261) evaluating the benefit of adjuvant gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU vs. surveillance has reported a significant improvement in disease-free survival in patients with pT2–pT4, N (any) or LN-positive (pT any, N1–3) M0 UTUC [246] (LE: 1).

The main limitation of using adjuvant chemotherapy for advanced UTUC remains the limited ability to deliver full dose cisplatin-based regimen after RNU, given that this surgical procedure is likely to impact renal

function [247, 248]. In a retrospective study histological variants of UTUC exhibit different survival rates and adjuvant chemotherapy was only associated with an OS benefit in patients with pure UC [249] (LE: 3).

7.1.3.2.2 Immunotherapy

In a phase 3, multicentre, double-blind RCT involving patients with high-risk muscle-invasive UC who had undergone radical surgery, adjuvant nivolumab improved disease-free survival compared to placebo in the intention-to-treat population (20.8 vs 10.8 months) and among patients with a PD-L1 expression level of 1% or more [250]. The median survival free from recurrence outside the urothelial tract in the intention-to-treat population was 22.9 months with nivolumab and 13.7 months with placebo. Treatment-related adverse events ≥ grade 3 occurred in 17.9% of the nivolumab group and 7.2% of the placebo group. The subgroup of patients with UTUC in this study needs further analysis to better understand the effect of adjuvant nivolumab for high-risk muscle-invasive UC after RNU.

*7.1.4 **Adjuvant radiotherapy after radical nephroureterectomy***

Adjuvant radiation therapy has been suggested to control loco-regional disease after surgical removal. The data remains controversial and insufficient for conclusions [251-254]. Moreover, its added value to chemotherapy remains questionable [253].

*7.1.5 **Post-operative bladder instillation***

The rate of bladder recurrence after RNU for UTUC is 22–47% [174, 224]. Two prospective randomised trials [255, 256] and two meta-analyses [257, 258] have demonstrated that a single post-operative dose of intravesical chemotherapy (mitomycin C, pirarubicin) 2–10 days after surgery reduces the risk of bladder tumour recurrence within the first years post-RNU (LE: 2). Prior to instillation, a cystogram might be considered in case of any concerns about drug extravasation.

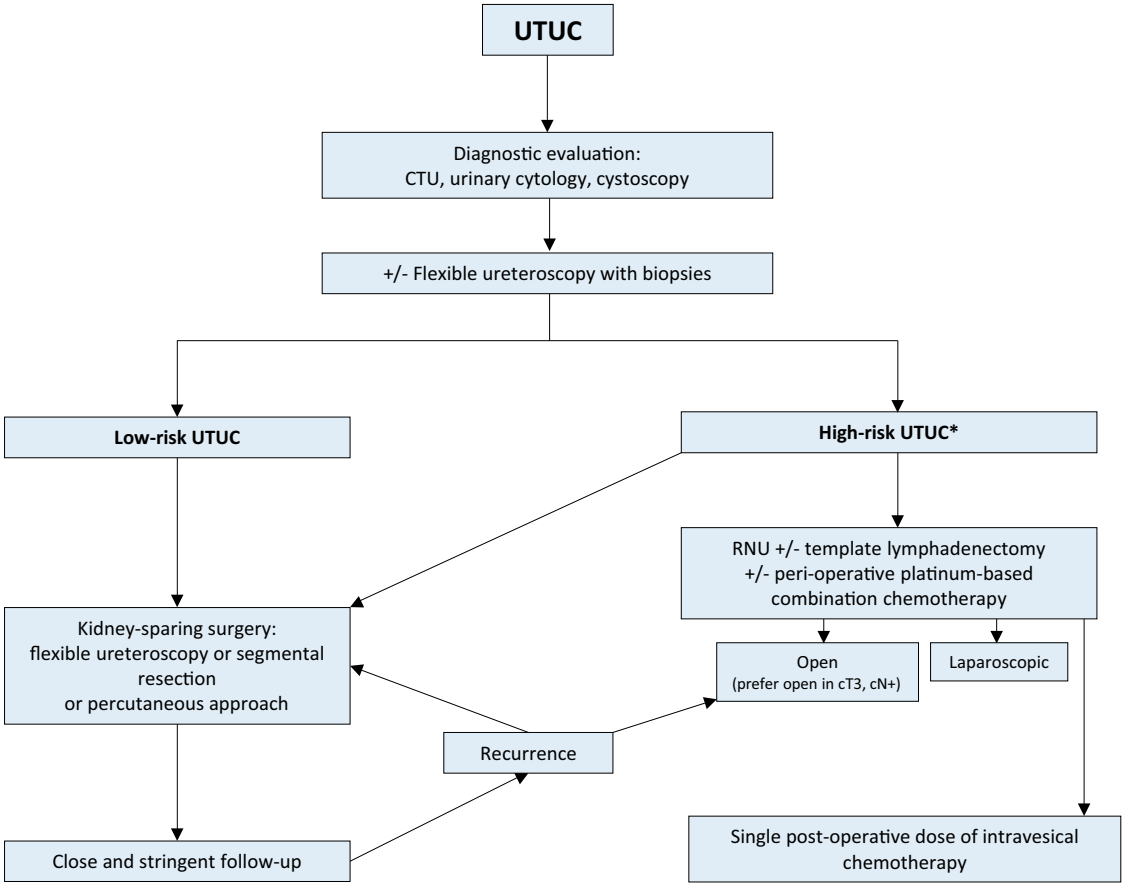
Based on current evidence it is unlikely that additional instillations beyond one peri-operative instillation of chemotherapy further substantially reduces the risk of intravesical recurrence [259]. Whilst there is no direct evidence supporting the use of intravesical instillation of chemotherapy after kidney-sparing surgery, single-dose chemotherapy might be effective in that setting as well (LE: 4). Management is outlined in Figures 7.1 and 7.2. One low-level evidence study suggested that bladder irrigation might reduce the risk of bladder recurrence after RNU [260].

*7.1.6 **Summary of evidence and guidelines for the management of high-risk non-metastatic UTUC***

Summary of evidence	**LE**
Radical nephroureterectomy is the standard treatment for high-risk UTUC, regardless of tumour location.	2a
Open, laparoscopic and robotic approaches have similar oncological outcomes for organ-confined UTUC.	2a
Failure to completely remove the bladder cuff increases the risk of bladder cancer recurrence.	3
Lymphadenectomy improves survival in muscle-invasive UTUC.	3
Post-operative chemotherapy improves disease-free survival.	1b
Single post-operative intravesical instillation of chemotherapy lowers the bladder cancer recurrence rate.	1

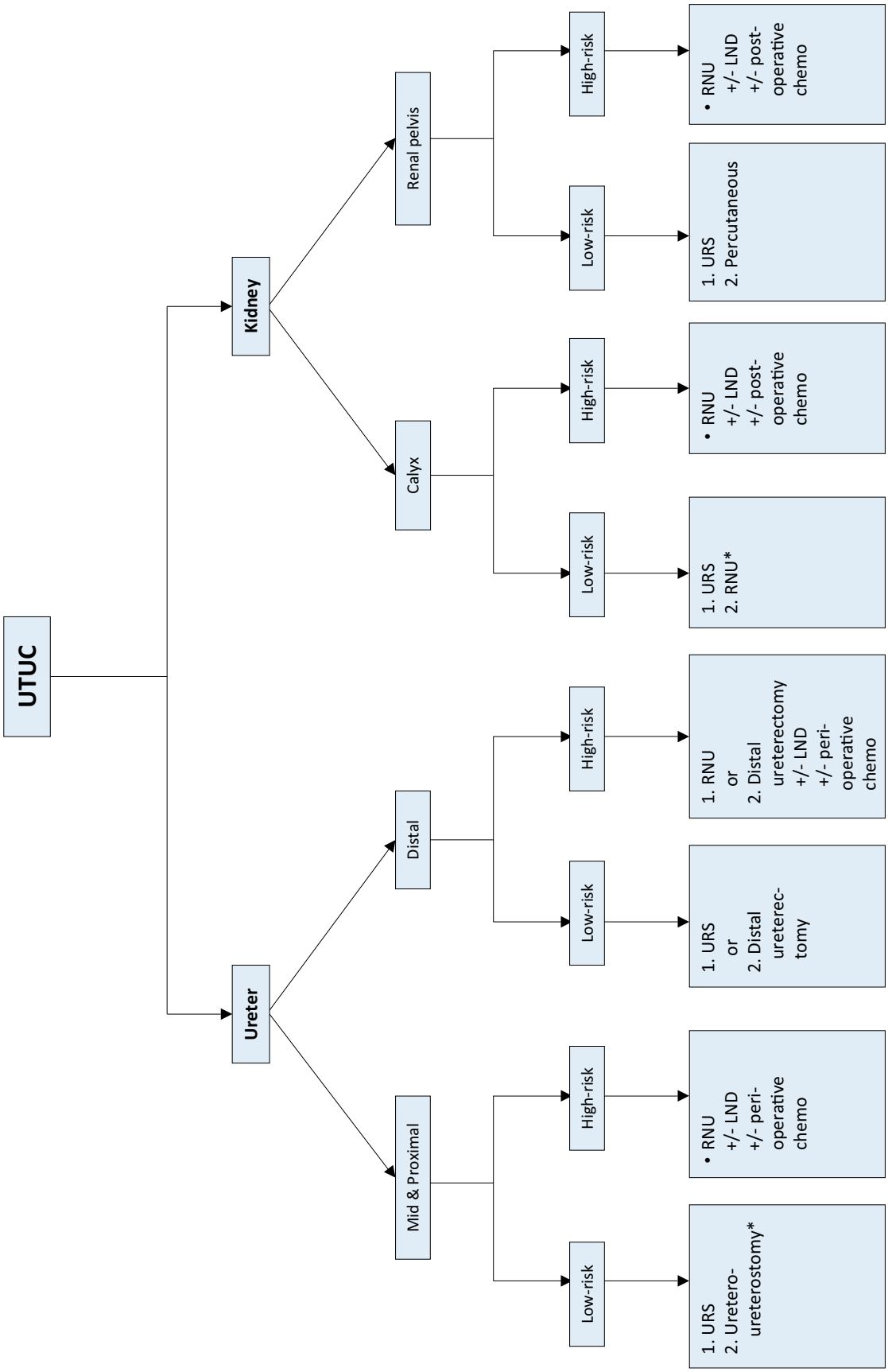
Recommendations	**Strength rating**
Perform radical nephroureterectomy (RNU) in patients with high-risk non-metastatic upper tract urothelial carcinoma (UTUC).	Strong
Perform open RNU in non-organ-confined UTUC.	Weak
Perform a template-based lymphadenectomy in patients with high-risk non-metastatic UTUC.	Strong
Offer post-operative systemic platinum-based chemotherapy to patients with high-risk non-metastatic UTUC.	Strong
Deliver a post-operative bladder instillation of chemotherapy to lower the intravesical recurrence rate.	Strong

Figure 7.1: Proposed flowchart for the management of UTUC



**In patients with solitary kidney, consider a more conservative approach.*
CTU = computed tomography urography; RNU = radical nephroureterectomy;
UTUC = upper urinary tract urothelial carcinoma.

Figure 7.2: Surgical treatment according to location and risk status



1 = first treatment option; 2 = secondary treatment option.
**In case not amendable to endoscopic management.*
LND = lymph node dissection; RNU = radical nephroureterectomy; URS = ureteroscopy;
UTUC = upper urinary tract urothelial carcinoma.

7.2 Metastatic disease

*7.2.1 **Radical nephroureterectomy***

The role of RNU in the treatment of patients with metastatic UTUC has recently been explored in several observational studies [261-264]. Although evidence remains very limited, RNU may be associated with cancer-specific [261, 263, 264] and OS benefit in selected patients, especially those fit enough to receive cisplatin-based chemotherapy [262, 263]. It is noteworthy that these benefits may be limited to those patients with only one metastatic site [263]. Nonetheless, given the high risk of bias of the observational studies addressing RNU for metastatic UTUC, indications for RNU in this setting should mainly be reserved for palliative patients, aimed at controlling symptomatic disease [18, 110] (LE: 3).

*7.2.2 **Metastasectomy***

There is no UTUC-specific study supporting the role of metastasectomy in patients with advanced disease. However, several reports including both UTUC and bladder cancer patients suggested that resection of metastatic lesions could be safe and oncologically beneficial in selected patients with a life expectancy of more than 6 months [265-267]. This was confirmed in the most recent and largest study to date [268]. In patients with metastases limited to lung and/or lymph nodes, whose disease responded to systemic chemotherapy, metastasectomy can improve oncological outcomes in individual cases [269] (LE: 3).

Nonetheless, in the absence of data from RCTs, patients should be evaluated on an individual basis and the decision to perform a metastasectomy (surgically) should be made following a shared decision-making process with the patient.

*7.2.3 **Systemic treatments***

7.2.3.1 First-line setting

7.2.3.1.1 Patients fit enough to tolerate cisplatin-based combination chemotherapy

Data from the bladder cancer literature and from small, single-centre UTUC studies suggest that platinum-based combination chemotherapy, especially cisplatin, is efficacious as first-line treatment of metastatic UTUC. Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin [2]. A number of cisplatin-containing chemotherapy regimens are acceptable although gemcitabine and cisplatin is the most widely used. A retrospective analysis of three RCTs showed that primary tumour location in the lower- or upper urinary tract had no impact on progression-free survival (PFS) or OS in patients with locally advanced or metastatic UC treated with platinum-based combination chemotherapy [270]. The efficacy of immunotherapy using programmed death-1 (PD1) or programmed death-ligand 1 (PD-L1) inhibitors has been evaluated in the first-line setting for the treatment of cisplatin-fit patients with metastatic UC, including those with UTUC [271]. The combination of platinum-based chemotherapy with immune checkpoint inhibitors have not resulted in positive significant survival advantages and are not currently recommended [272].

7.2.3.1.2 Patients fit for carboplatin (but unfit for cisplatin-based combination chemotherapy)

Carboplatin-based chemotherapy is recommended in patients unfit for cisplatin [2]. Carboplatin with gemcitabine is the preferred regimen [273].

7.2.3.1.3 Maintenance therapy after first-line platinum-based treatment

Platinum-based chemotherapy followed by maintenance avelumab is preferred to upfront immune checkpoint inhibitors in both PD-L1 biomarker positive and negative patients. Data from a phase III RCT showed that the use of avelumab maintenance therapy after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin (started within 10 weeks of completion of first-line platinum-based chemotherapy) significantly prolonged OS as compared to best supportive care alone in those patients with advanced or metastatic UC who did not progress during, or responded to, first-line chemotherapy (HR 0.69; 95% CI 0.56–0.86) [274, 275]. An increase in median OS from 14 to 21 months was observed with avelumab. Although no subgroup analysis based on tumour location was available in this study, almost 30% of the included patients had UTUC. Similarly, in a phase II study comprising 108 patients with metastatic UC achieving at least stable disease on first-line platinum-based chemotherapy, maintenance pembrolizumab improved PFS compared to placebo (5.4 vs. 3.0 months) [276].

7.2.3.1.4 Immunotherapy in cisplatin-unfit patients

Pembrolizumab or atezolizumab are alternative choices for patients who are PD-L1 positive and not eligible for cisplatin-based chemotherapy, although RCTs failed to show significant superiority compared with chemotherapy [272, 277]. Final data from randomised trials with durvalumab are similar with no OS benefit [278]. Biomarkers (SP142 for atezolizumab; 22C3 for pembrolizumab) should be used to match the drug, as recommended by the European Medicines Agency (EMA) [279, 280].

In a single-arm phase II trial (n = 370) of cisplatin-ineligible UC, pembrolizumab monotherapy was

associated with an objective response rate of 26% in 69 metastatic UTUC patients [281]. In the overall cohort, a PD-L1 expression of 10% was associated with a greater response rate to pembrolizumab. Treatment-related toxicity was in line with previous studies. In a single-arm phase II trial (n = 119) of cisplatin-ineligible UC, atezolizumab monotherapy was associated with an objective response rate of 39% in 33 (28%) metastatic UTUC patients [282]. Median OS in the overall cohort was 15.9 months and treatment-related toxicity was in line with previous studies. Data from a phase III RCT including 1,213 patients with metastatic cisplatin-eligible and cisplatin-ineligible UC, of which 312 (26%) were diagnosed with UTUC, showed that the combination of atezolizumab with platinum-based chemotherapy prolonged both PFS and OS [277]. No subgroup analysis based on tumour location was performed in this study.

7.2.3.2 Second-line setting

7.2.3.2.1 Immunotherapy

A phase III RCT including 542 patients who received prior platinum-based chemotherapy for advanced UC showed that pembrolizumab could decrease the risk of death compared to second-line chemotherapy (the investigator's choice of paclitaxel, docetaxel, or vinflunine); median OS: 10.3 months for pembrolizumab and 7.4 months for chemotherapy, HR 0.73, 95% CI: 0.59–0.91 [283]. Responses were more frequent and durable for pembrolizumab compared with chemotherapy (21% vs. 11%). In the UTUC subgroup (n = 75, 13.8%), the OS benefit seemed larger (50%).

The IMVigor211 trial explored atezolizumab in PD-L1 biomarker positive tumours in patients with tumours which have relapsed after platinum-based therapy and failed to show a significant OS advantage [284].

In a phase II study, 48 patients with platinum-refractory UC (18/48 patients with UTUC) were treated with cabozantinib. There was one complete response and 7 partial responses (objective response rate 19%, 95% CI: 9–34). Median PFS was 3.7 months (95% CI: 3–6) [285].

Other immunotherapies such as nivolumab [286], avelumab [287, 288] and durvalumab [289] have shown objective response rates ranging from 17.8% [289] to 19.6% [286] and median OS ranging from 7.7 months to 18.2 months in patients with platinum-resistant metastatic UC. These results were obtained from single-arm phase I or II trials only and the number of UTUC patients included in these studies was only specified for avelumab (n = 7/15.9%) without any subgroup analysis based on primary tumour location [288].

The immunotherapy combination of nivolumab plus ipilimumab has shown significant anti-tumour activity with objective response rate up to 38% in a phase I/II multicentre trial including 78 patients with metastatic UC progressing after platinum-based chemotherapy [290]. Although UTUC patients were included in this trial, no subgroup analysis was available. Other immunotherapy combinations may be effective in the second-line setting but data are currently limited [291].

7.2.3.2.2 Novel agents

Fibroblast growth factor receptors (FGFR) inhibition

Erdafitinib, a pan-FGFR tyrosine kinase inhibitor of *FGFR1–4*, was associated with a 40% response rate in a phase II trial in 99 patients with locally advanced or metastatic UC who progressed after first-line chemotherapy and harboured a FGFR DNA genomic alterations (*FGFR2* or *3* mutations, or *FGFR3* fusions) [292]. This study included 23 UTUC patients with visceral metastases showing a 43% response rate.

Antibody drug conjugates (ADC)

A phase II study enrolled 89 patients (of whom 43% had UTUC) with metastatic UC progressing after therapy with PD-1 or PD-L1 inhibitors. All patients received the antibody–drug conjugate enfortumab vedotin. The objective response rate was 52%, 20% of patients achieved complete response [293].

7.2.3.3 Third-line setting

In an open-label phase II trial a total of 108 patients with metastatic UC with progression on platinum-based and checkpoint inhibitors were treated with the antibody-drug conjugate sacituzumab govitecan. The objective response rate was 27%, with median duration of response 7.2 months, median PFS 5.4 months and OS 10.9 months. The site of primary UC is not mentioned in the publication [294].

A pre-planned subgroup analysis from the phase III RANGE trial assessed the impact on outcomes and safety of ramucirumab added to docetaxel after disease progression on both platinum and immune checkpoint inhibitors therapy [295]. Median PFS was 3.15 months on ramucirumab/docetaxel vs 2.73 months on placebo/docetaxel (HR = 0.786, 95%, CI: 0.404–1.528, p = 0.4877). This trend for ramucirumab benefit occurred despite the ramucirumab arm having a higher percentage of patients with poorer prognosis. However, these findings need confirmation by further studies, as this analysis is limited by patient numbers and an imbalance in the treatment arms.

7.2.4 *Summary of evidence and guidelines for the treatment of metastatic UTUC*

Summary of evidence	LE
Radical nephroureterectomy may improve quality of life and oncologic outcomes in select metastatic patients.	3
Cisplatin-based combination chemotherapy can improve median survival.	2
Cisplatin-containing combination chemotherapy is standard in advanced or metastatic patients fit enough to tolerate cisplatin.	1b
Single-agent and carboplatin-based combination chemotherapy are less effective than cisplatin-based combination chemotherapy in terms of complete response and survival.	3
Non-platinum combination chemotherapy has not been tested against standard chemotherapy in patients who are fit or unfit for cisplatin combination chemotherapy.	4
Maintenance avelumab is associated with an OS advantage compared with best supportive care in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin or carboplatin.	1b
PD-1 inhibitor pembrolizumab has been approved for patients who have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase III trial.	1b
PD-L1 inhibitor atezolizumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor nivolumab has been approved for patients that have progressed during or after previous platinum-based chemotherapy and did not receive previous immune therapy based on the results of a phase II trial.	2a
PD-1 inhibitor pembrolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of pembrolizumab is restricted to PD-L1 positive patients.	2a
PD-L1 inhibitor atezolizumab has been approved for patients with advanced or metastatic UC ineligible for cisplatin-based first-line chemotherapy based on the results of a phase II trial but use of atezolizumab is restricted to PD-L1 positive patients.	2a
Erdafitinib improves OS in in platinum-refractory patients with locally advanced or metastatic UC and FGFR DNA genomic alterations (*FGFR2* or *3* mutations, or *FGFR3* fusions).	2a

Recommendations	Strength rating
Offer radical nephroureterectomy as a palliative treatment to symptomatic patients with resectable locally advanced tumours.	Weak
First-line treatment for cisplatin-eligible patients	
Use cisplatin-containing combination chemotherapy with GC or HD-MVAC.	Strong
Do not offer carboplatin or non-platinum combination chemotherapy.	Strong
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus cisplatin.	Strong
First-line treatment in patients unfit for cisplatin	
Offer checkpoint inhibitors pembrolizumab or atezolizumab depending on PD-L1 status.	Weak
Offer carboplatin combination chemotherapy if PD-L1 is negative.	Strong
Use maintenance avelumab in patients who did not have disease progression after 4 to 6 cycles of gemcitabine plus carboplatin.	Strong
Second-line treatment	
Offer checkpoint inhibitor (pembrolizumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer checkpoint inhibitor (atezolizumab or nivolumab) to patients with disease progression during or after platinum-based combination chemotherapy for metastatic disease.	Strong
Offer erdafitinib in platinum-refractory tumours with FGFR alterations.	Strong
Only offer vinflunine to patients for metastatic disease as second-line treatment if immunotherapy or combination chemotherapy is not feasible. Alternatively, offer vinflunine as third- or subsequent-line treatment.	Strong

GC = gemcitabine plus cisplatin; FGFR = fibroblast growth factor receptors; HD-MVAC = high-dose intensity methotrexate, vinblastine, adriamycin plus cisplatin; PD-L1 = programmed death ligand 1; PCG = paclitaxel, cisplatin, gemcitabine.

8. FOLLOW-UP

The risk of recurrence and death evolves during the follow-up period after surgery [296]. A direct relationship exists between event-free follow-up and survival probability after RNU [137]. Stringent follow-up is mandatory to detect metachronous bladder tumours (probability increases over time [297]), local recurrence, and distant metastases.

Surveillance regimens are based on cystoscopy and urinary cytology [15, 297]. Bladder recurrence is not considered a distant recurrence. When kidney-sparing surgery is performed, the ipsilateral UUT requires careful and long-term follow-up due to the high risk of disease recurrence [195, 298, 299] and progression to RNU beyond 5 years [300]. Despite endourological improvements, follow-up after kidney-sparing management is difficult and frequent, and repeated endoscopic procedures are necessary. Following kidney-sparing surgery, and as done in bladder cancer, an early repeated (second look) ureteroscopy within 6 to 8 weeks after primary endoscopic treatment has been proposed, but is not yet routine practice [2, 196]. Section 8.1 presents the summary of evidence and recommendations for follow-up of UTUC.

8.1 Summary of evidence and guidelines for the follow-up of UTUC

Summary of evidence	LE
Follow-up is more frequent and more stringent in patients who have undergone kidney-sparing treatment compared to radical nephroureterectomy.	3

Recommendations	Strength rating
After radical nephroureterectomy	
Low-risk tumours	
Perform cystoscopy at three months. If negative, perform subsequent cystoscopy 9 months later and then yearly, for 5 years.	Weak
High-risk tumours	
Perform cystoscopy and urinary cytology at 3 months. If negative, repeat subsequent cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Perform computed tomography (CT) urography and chest CT every 6 months for 2 years, and then yearly.	Weak
After kidney-sparing management	
Low-risk tumours	
Perform cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years.	Weak
Perform ureteroscopy (URS) at 3 months.	Weak
High-risk tumours	
Perform cystoscopy, urinary cytology, CT urography and chest CT at 3 and 6 months, and then yearly.	Weak
Perform URS and urinary cytology *in situ* at 3 and 6 months.	Weak

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10. CONFLICT OF INTEREST

All members of the Non-Muscle-Invasive Bladder Cancer Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is available on the European Association of Urology website: http://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/.

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urethral Strictures Guidelines aim to provide a comprehensive overview of urethral strictures in male, female, and transgender patients. The Panel is aware of the geographical variations in healthcare provision.

It must be emphasised that guidelines present the best evidence available to the experts; however, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urethral Strictures Guidelines panel consists of an international multidisciplinary group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/urethral-strictures/.

1.3 Available publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents can be viewed through the EAU website: http://www.uroweb.org/guideline/urethral-strictures/. A list of supplementary tables supporting this text can also be found online, along with an appendix of abbreviations specific to this text: https://uroweb.org/guideline/urethralstrictures/?type=appendices-publications.

1.4 Publication history

This document is a new Guideline first published in 2021. Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

1.5 Summary of Changes

This 2022 guideline represents a limited updated of the original 2021 text. References have been updated and now refer the reader to the final versions of the Panel's summary and systematic review papers. Minor grammatical and formatting issues have also been addressed.

2. METHODOLOGY

2.1 Methods

For the 2021 Urethral Strictures Guidelines, new and relevant evidence was identified, collated, and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2008 and 2019 and restricted to English language publications. The panel defined by consensus inclusion and exclusion criteria for each topic before the scope search. Detailed search strategies are available online: https://uroweb.org/guideline/urethral-strictures/.

Relevant literature prior to the 2008 scope search cut-off was allowed if it was estimated to be of exceptional value by the panel. Relevant literature after the 2019 scope search cut-off was searched for by the panel member dedicated to a specific topic.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);

3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternatives.

The Panel wants to highlight that "success" in urethral stricture treatment is poorly defined and subjective. "Success" is usually defined as urethral patency, either subjective by the absence of voiding symptoms or objective by imaging or urethral calibration. Despite urethral patency, the patient themselves might not consider the treatment as successful because of functional consequences (e.g., post-void dribbling, erectile/ejaculatory dysfunction, altered genital appearance). In this Guideline, the Panel agreed to avoid the term "success". Instead, the term "patency rate" or "stricture recurrence rate" will be used to clarify that only stricture recurrence was taken into consideration (as assessed by the authors).

The Panel would like to stress that patency after urethral surgery is dependent on the general principles of wound healing. These principles have stood the test of time and need to be respected [5]. Some examples:

- An anastomosis should be made between healthy urethral ends and without any tension.
- A graft requires a well-vascularised graft bed with a close contact between the graft and graft bed to promote imbibition and inosculation.
- If the full circumference of the urethral mucosa is destroyed, spontaneous regeneration will not take place.
- Contraction and fibrosis in a wound only stops after it is covered by its epithelium.

The Panel conducted two systematic reviews (SR) to support guideline recommendations, which were published in 2021:

- What is the role of single-stage oral mucosa graft urethroplasty in the surgical management of Lichen Sclerosus-related stricture disease in men? A systematic review [6];
- Free Graft Augmentation Urethroplasty for Bulbar Urethral Strictures: Which Technique Is Best? A Systematic Review [7].

The results of these reviews are included in the 2022 Urethral stricture guidelines.

In addition, the panel drafted three summary papers of the guidelines which were published in European Urology and European Urology Focus:

- EAU guidelines on urethral stricture disease (part 1): management of male urethral stricture disease [8];
- EAU Guidelines on urethral stricture disease (part 2): diagnosis, perioperative management, and follow-up in males [9];
- EAU guidelines on urethral stricture disease (part 3): management of strictures in females and transgender patients [10].

2.2 Review

The Urethral Strictures Guidelines were peer reviewed prior to initial publication in 2021.

2.3 Future goals

A further SR was conducted in 2021 and will see publication in 2022:

- Is a course of intermittent self-dilatation (ISD) with topical corticosteroids superior at stabilising urethral stricture disease in men and improving functional outcomes over a course of ISD alone?

An update of the strictures guideline will be conducted when deemed necessary, but at latest after five years. Further SRs will be conducted after approval of the Guidelines Office.

3. DEFINITION, EPIDEMIOLOGY, AETIOLOGY AND PREVENTION

3.1 Definitions

In males, a urethral stricture refers to a narrowed segment of the anterior urethra due to a process of fibrosis and cicatrisation of the urethral mucosa and surrounding spongiosus tissue ("spongiofibrosis") [11, 12]. In the male posterior urethra, there is no spongiosus tissue and at this location the terms stenosis is preferred [11, 12]. The definition of meatal stenosis is generally accepted as a short distal narrowing at the meatus, without involvement of the fossa navicularis [12].

There is no universal definition for what constitutes a female urethral stricture (FUS). Female urethral stricture is defined by most authors as a 'fixed anatomical narrowing' causing reduced urethral calibre [13, 14]. This reduced urethral calibre is variously defined as between < 10 Fr to < 20 Fr [15, 16] with the majority of series defining < 14 Fr as diagnostic, compared with a 'normal' urethral calibre of 18-30 Fr.

In transgender patients, the term stricture is also used to define a narrowing of the reconstructed urethra despite the absence of surrounding spongious tissue.

3.2 Epidemiology

In males, a sharp increase in incidence is observed after the age of 55 years, with a mean age of 45.1 [17, 18]. Overall, the incidence is estimated to be 229-627 per 100,000 males [17]. The anterior urethra is most frequently affected (92.2%), in particular the bulbar urethra (46.9%) [18].

In females, 2-29% of patients presenting with refractory lower urinary tract symptoms (LUTS) have bladder outflow obstruction (BOO) [19-22] of whom 4-20% will have a urethral stricture [21-23]. True FUS therefore occurs in 0.08-5.4% of women with refractory LUTS. There is a markedly increased incidence in women over 64 years of age [24].

In children, most strictures are traumatic: related to iatrogenic causes in 27.8-48% and external trauma in 34-72% [25]. Less frequent congenital (13%), inflammatory (4%), or post-infectious strictures (1%) are seen. The bulbar urethra is the most frequently affected part of the urethra [25].

After hypospadias repair, meatal stenosis and urethral strictures are reported in 1.3-20% of cases, depending on the severity of the hypospadias and the technique used [26]. There is a significantly higher incidence of this type of strictures in well-resourced countries due to a higher surgical repair rate [27].

Up to 18% of all urethral strictures have been reported to involve the meatus or fossa navicularis, usually due to failed hypospadias repair (FHR), lichen sclerosus (LS), trauma/instrumentation or idiopathic causes [28-31].

Meatal stenosis post-circumcision has been reported in less than 0.2% of children undergoing circumcision as neonates [17].

In female-to-male (FtM) transgender patients ("trans men"), approximately 51% will suffer a urethral stricture [32]. Strictures almost exclusively arise at the neomeatus in male-to-female (MtF) transgender patients ("trans women") and occur in 14.4% of cases [33].

3.3 Aetiology and prevention

Stricture aetiology differs significantly throughout different regions in the world, due to differences in healthcare quality and environmental and practice patterns [27]. Regardless of geography, urethral stricture disease adversely impacts physical health and quality of life (QoL) [34, 35], notwithstanding costs associated with the treatment of primary and recurrent disease [36, 37]. The rationale for preventing urethral strictures is to avoid morbidity to the individual and costs to society. Prevention of urethral strictures encompasses reducing the causes of stricture (e.g., infection, trauma, iatrogenic injury) and where this is not possible, mitigating the risk.

*3.3.1 **Aetiology and prevention in males***

a. Sexually transmitted infection

Urethritis due to sexually transmitted infection (STI), in particular gonorrhoea, was previously a major cause of urethral strictures in well-resourced countries accounting for 40% of all cases [38]. The wide-scale promotion of safe sexual practices and easier access to sexual health services, resulting in timely treatment with

antimicrobials, is thought to have led to the considerable reduction in the problem [38]. Infective urethritis now accounts for 0.9% to 3.7% of cases in contemporary series from well-resourced countries [38, 39] but continues to be the major cause of strictures in low-resourced countries comprising 41.6% of all strictures [40].

Summary of evidence	LE
Access to investigation and treatment of STI is associated with a temporal decline in the incidence of infective urethritis related strictures.	3

Recommendation	Strength rating
Advise safe sexual practices, recognise symptoms of sexually transmitted infection, and provide access to prompt investigation and treatment for men with urethritis.	Strong

b. Inflammation

Lichen sclerosus involves the urethra in 20% of cases [41] and is the most common cause of panurethral stricture disease (48.6%) [18]. The aetiology of LS has not been fully elucidated but is thought to have an autoimmune origin [42]. Lichen sclerosus may be associated with environmental factors and non-autoimmune comorbidities. Uncircumcised men are far more likely to suffer LS than circumcised men (age-adjusted odds ratio [OR] of 53.55; 95% confidence interval [CI]: 7.24-395.88) [43]. Lichen sclerosus is also associated with higher mean body mass index (BMI), diabetes mellitus, coronary artery disease, tobacco usage, hyperlipidaemia, and hypertension [44-46].

c. External urethral trauma

External trauma to the urethra is the second most common cause of stricture formation in adults [38]. The urethra is vulnerable to trauma during certain activities including sport, driving a vehicle, sexual intercourse and during combat. The bulbar urethra is the site most frequently affected by blunt trauma [12], usually as a result of straddle injuries or kicks to the perineum. Penile fracture is associated with a urethral injury in 15% of cases [47]. Motor vehicle accidents are the main cause of blunt injuries to the posterior urethra associated with pelvic fractures [48]. Penetrating injuries of the urethra are uncommon during non-combat situations [49].

d. Iatrogenic urethral injury

Iatrogenic injury to the urethra is one of the most common causes of strictures in well-resourced countries [18, 38] accounting for 32-79% of all strictures [38, 50]. In children, specifically iatrogenic causes were identified in 6.7-25% of cases [51]. Preventing iatrogenic urethral injury represents the main way in which urologists can prevent urethral strictures. Iatrogenic urethral injury most commonly results from urethral instrumentation (e.g., catheterisation, cystoscopy), surgery for benign prostatic obstruction (BPO), surgery for prostate cancer, or radiotherapy [39].

d.1 Urethral catheterisation

Urethral strictures are a recognised complication of urethral catheterisation accounting for 11.2-16.3% of all strictures [18, 38]. In a meta-analysis by Hollingsworth *et al.*, the pooled percentage of patients who developed urethral stricture or erosion after short-term catheterisation (< 3 weeks) in higher-quality studies was 3.4% (CI: 1-7%) [52]. In studies comprised mainly of men with spinal cord injury with indwelling urethral catheters, the pooled estimate of urethral stricture or erosion was 8.7% (CI: 0.0-18.7%) [52].

Urethral strictures following catheterisation may arise as a consequence of injury during attempts at insertion or during the period a catheter remains *in situ*. During insertion, the urethra may be injured by formation of a false passage by the catheter tip (29.7%) or inflation of the balloon within its lumen (70.3%) [53]. The rate of urethral injuries due to catheterisation was found to be 3.2 per 1,000 inpatients [54]. A six-month prospective multicentre study found that of 37 patients with catheter-related urethral trauma referred to urologists, 24% continued to perform ISD once weekly and 11% required at least one urethral dilation for urethral stricture [55]. In another follow-up study of 37 patients with catheter-related urethral trauma, 78% of patients developed urethral stricture [53]. The most common locations of trauma are the bulbar and posterior urethra [56].

Catheter-related trauma can be prevented through several measures [57]. Studies have indicated around 25% of all indwelling catheterisations in hospitals were unnecessary and inappropriate [58, 59]. Implementation of guidelines [60, 61] and specific criteria [62] have been shown to reduce catheterisation rates. Several studies have identified deficits in the knowledge of urethral catheterisation amongst resident doctors [63, 64]. This is postulated to be a factor in catheter-related trauma [64]. A targeted training program on urethral catheterisation

for nursing staff was shown to be effective in reducing iatrogenic urethral injuries in a prospective single institution study [54].

In addition to guidance and education, another approach to safer catheterisation is modification of the standard Foley catheter. A novel catheter balloon pressure valve safety system was developed to prevent balloon inflation injury though this has not been assessed in comparative studies [65, 66]. Bugeja *et al.,* studied the use of urethral catheterisation device (UCD) incorporating a guidewire, in prospective observational cohort study that included 174 patients. The incidence of adverse events was 7% with standard Foley catheterisation vs. 0% with the UCD (no statistical analysis was performed) [67]. A further prospective observational study found that Seldinger technique catheterisation could be used successfully by non-urology trained doctors [68]. These technologies need to be further assessed in prospective raondomised controlled trials (RCTs), incorporating cost-benefit analysis.

Catheter diameter is suggested as a possible contributing factor to urethral stricture due to a pressure effect on the urethral wall [69]. Decreasing the catheter size from 22 Fr to 18 Fr significantly decreased the risk of fossa navicularis strictures (6.9% vs. 0.9%, p=0.02) after radical prostatectomy (RP) [70]. Catheter material may also have an influence on the occurrence of stricture. In the 1970s/80s several comparative studies in patients undergoing cardiac surgery demonstrated that non-coated latex catheters were associated with a greater incidence of urethritis and more stricture formation than silicone catheters [71-73]. Other studies showed no difference [74-76]. Modern latex catheters have polymeric coatings [77] due to the concern with regards to stricture alongside the risk of hypersensitivity and the demonstrable *in vitro* toxicity of latex. Prolonged urethral catheterisation has also been implicated in the aetiology of stricture (e.g., poly-trauma, burns patients) [50].

Summary of evidence	**LE**
A significant proportion of catheter insertions in hospitalised patients were considered unnecessary.	2b
Educational programs can reduce the incidence of catheter-related urethral injury.	2a
Larger catheter size was associated with a greater risk of navicular fossa strictures.	3
Non-coated latex catheters are associated with a greater degree of urethritis and possibly a greater risk of urethral strictures, than non-latex catheters or coated latex catheters.	1a

Recommendations	**Strength rating**
Avoid unnecessary urethral catheterisation.	Strong
Implement training programmes for physicians and nurses performing urinary catheterisation.	Strong
Do not use catheters larger than 18 Fr if urinary drainage is the only purpose.	Weak
Avoid using non-coated latex catheters.	Strong

d.2 Transurethral prostate surgery

Urethral stricture following transurethral prostate surgery occurs in between 4.5-13% of patients [78], whereas bladder neck stenosis (BNS) occurs in between 0.3-9.7% [79]. Transurethral surgery is the most common cause of iatrogenic urethral stricture accounting for 41% of all causes [50]. The most common location for urethral stricture is the bulbomembranous urethra, followed by the fossa navicularis and penile urethra [80, 81]. Postulated mechanisms include friction at the penoscrotal junction, lack of adequate lubrication, repetitive 'in and out' movement of the resectoscope, breach of mucosal integrity leading to urine extravasation and monopolar current leak due to inadequate resectoscope insulation [82]. Bladder neck stenosis may be related to excessive and/or circumferential resection and the use of relatively large resection loops which may generate excessive heat in small intraurethral adenomas leading to scarring [79, 83]. Stenoses of the posterior urethra may also be due to a prolonged period of post-operative inability to void [84].

d.2.1 Risk factors for development of urethral stricture and bladder neck stenosis

Several risk factors for the development of urethral stricture and BNS following transurethral prostate surgery have been identified. Both prostatic inflammation (OR: 4.31) and operative time > 60 min (OR: 4.27) were found to be independent predictors of stricture after monopolar transurethral resection of prostate (TURP) [85]. In terms of bipolar TURP, slower resection rate (OR: 0.003), intraoperative urethral mucosa rupture (OR: 2.44) and post-operative infection were shown to be independent predictors (OR: 1.49) [86, 87]. A larger-calibre endoscopic sheath (26 Fr vs. 24 Fr) was associated with a greater risk of bulbar urethral stricture following monopolar TURP (11.4% vs. 2.9%, p=0.018) [88]. Room temperature irrigation solution was associated with a greater risk of urethral stricture following combined transurethral resection and vaporisation of the prostate compared to body temperature irrigation (21.3% vs. 6.3%, p=0.002) [89].

Bladder neck stenosis is known to occur more frequently in smaller prostate glands after both monopolar and bipolar TURP [90, 91]. Lee *et al*., found that adenoma weight was an independent risk factor for BNS after monopolar TURP [91]. Meanwhile, Tao *et al*., found total prostate volume (< 46.2 g) (OR: 1.5), but not resected gland weight, to be an independent risk factor [86].

d.2.2 Incidence of urethral stricture and bladder neck stenosis with different energy modalities

A SR and meta-analysis by Cornu *et al*., showed no significant differences in urethral stricture and BNS rates by energy modality (monopolar, bipolar, holmium laser enucleation, photoselective vaporisation) [78]. In another meta-analysis assessing outcomes of thulium (Tm:Yag) laser and bipolar TURP, no difference in urethral stricture and BNS rates were found between the two modalities [92]. The presence of potentially confounding factors such as endoscopic sheath diameter, energy setting used, procedural length and length of follow-up make inter-study comparisons between energy modalities problematic. Overall, there is no strong evidence that any single modality is associated with a clinically significant higher incidence of urethral stricture and BNS than others. Selection of modality should be based on a comprehensive evaluation of clinical safety and efficacy. A summary of incidences of urethral stricture and BNS with different modalities is presented in Table 3.1.

Table 3.1: Incidence of urethral stricture and bladder neck stenosis by transurethral modality (adapted from Chen *et al*. 2016 [79]**)**

Modality	Urethral stricture	Bladder neck stenosis
Transurethral resection of prostate (TURP) - monopolar and bipolar	1.7-11.7%	2.4-9.7%
Holmium enucleation of the prostate (HoLEP)	1.4-4.4%	0-5.4%
Photo-selective vaporisation (PVP)	0-4.4%	1.4-3.6%

d.2.3 Interventions to prevent urethral stricture and bladder neck stenosis

Sciarra and colleagues conducted a single-blind RCT (n=96) to assess the use of rofecoxib for stricture prevention following TURP. At twelve months follow-up a urethral stricture was found in 17% and 0% of cases in the placebo and rofecoxib groups, respectively (p=0.0039) [93]. Chung *et al*., conducted a single blinded RCT (n=180) evaluating the effect of urethral instillation of hyaluronic acid (HA) and carboxymethylcellulose (CMC). Urethral stricture on urethrography was diagnosed in 1.25% and 8.64% of patients in the treatment and placebo group respectively (p=0.031). Further RCTs are needed to confirm these findings and the safety of the pharmacological interventions.

Several earlier comparative studies assessed whether routine preliminary urethrotomy with an Otis urethrotome prevented the incidence of stricture following TURP [94-97]. Only one of these reported at least twelve-month follow-up, finding no significant difference in stricture rate in patients undergoing TURP alone vs. Otis urethrotomy followed by TURP (21% vs. 14%) [98]. Others have suggested performing internal urethrotomy where there are pre-existent meatal or urethral strictures [99].

Adjunctive transurethral incision of the prostate (TUIP) at the end of TURP to reduce the rates of BNS was studied by Lee *et al.* [91]. A total of 1,135 patients of whom 667 underwent TURP and 468 underwent TURP plus TUIP were retrospectively studied. At median follow-up of 38 months, the incidence of BNS was 12.3% for the TURP group vs. 6.0% for the TURP plus TUIP group ($p < 0.001$). In glands < 30 g, the incidence of BNS in the TURP vs. the TURP plus TUIP group was 19.3% and 7.7%, respectively ($p < 0.05$). The clinical efficacy and safety of additional surgical interventions to prevent urethral stricture and BNS need to be confirmed in larger prospective RCTs before their use can be recommended.

Summary of evidence	LE
An RCT with more than twelve months follow-up failed to demonstrate a significant reduction in stricture rate using routine urethrotomy prior to TURP.	1b

Recommendation	Strength rating
Do not routinely perform urethrotomy when there is no pre-existent urethral stricture.	Strong

d.3 Radical prostatectomy

Radical prostatectomy has been associated with vesico-urethral anastomosis stricture (VUAS) in 0.5-30% of patients [79], though most modern series report it in the range of 1-3% [100]. The risk of stricture formation after salvage RP is notably higher (22-40%) [101]. Most VUAS develop within the first two years [101, 102]. A 2012 meta-analysis by Tewari *et al*., showed no significant difference in VUAS between open-, laparoscopic and robotic RP [103]. In contrast, a more recent analysis of a national cohort in the UK found that VUAS rate after robotic RP was 3.3%, which is significantly lower than following laparoscopic (5.7%) or open RP (6.9%) [104]. These findings are consistent with an earlier similar study conducted in the USA [105]. The difference in VUAS rates may be explained by the level of experience and surgical volume of surgeons [106]. The cohort studies represent "real world" data, including all levels of surgical experience and surgical volumes whereas the meta-analysis is based on clinical studies. Thus, the better outcomes for robotic RP in the population studies may be related to the shorter learning curve [107].

d.3.1 Risk factors for development of vesicourethral anastomosis strictures

These include higher grade cancer, more advanced stage, higher prostate volume, coronary artery disease, obesity, hypertension, diabetes mellitus, previous bladder outlet surgery and older age [100, 108, 109]. Surgical factors include the use of non-nerve-sparing technique, anastomotic urine leak, increased operative time and increased estimated blood loss [100, 108, 109]. In addition, low-volume surgeons (< 40/year) were shown to have higher VUAS rates, 27.7%, compared to high-volume surgeons (> 40/year), 22% [110].

d.3.2 Interventions to prevent vesicourethral anastomosis strictures

Srougi *et al*., studied bladder neck mucosal eversion in a prospective RCT of 95 patients. No significant difference was found in rates of VUAS at twelve months follow-up [111]. A meta-analysis by Kowelewski *et al*., comparing interrupted vs. continuous vesico-urethral anastomosis suturing found no difference in VUAS rates [112]. Another SR by Bai *et al*., compared barbed sutures to conventional sutures, and although heterogeneity across studies precluded meta-analysis, no patients developed VUAS with either approach [113].

d.4 Prostate radiation and ablative treatments

Urethral strictures occur in 1.5% of patients undergoing external beam radiation therapy (EBRT), 1.9% having brachytherapy (BT) and 4.9% who receive combination EBRT-BT at around four years follow-up [114]. These strictures typically occur in the bulbomembranous urethra [115]. As opposed to RP, stricture incidence after irradiation increases with time [101, 114]. For the ablative treatments, the stricture incidence after cryotherapy and high-intensity focused ultrasound (HIFU) is 1.1-3.3% and 1-31%, respectively [101]. The use of these treatment modalities in the salvage setting is associated with increased risk of stricture formation: 3-10% after salvage EBRT, 5-12% after salvage cryotherapy and 15-30% after salvage HIFU [101]. Due to the increasing utilisation of prostate irradiation (EBRT, BT) and ablative treatments (cryotherapy, HIFU), an increasing number of respectively radiation-induced and ablative treatment-induced strictures are expected [116].

d.4.1 Risk factors for the development of radiation strictures

Awad *et al*., performed a multivariate meta-regression analysis including 46 studies, finding combining ERBT + BT and length of follow-up to be significant predictors of urethral stricture following prostate radiation [114]. Factors not shown to predict urethral stricture included biochemical equivalent dose, age, and androgen deprivation therapy [114]. Previous TURP was not included in the analysis, but has been found to be an independent predictor of stricture (HR: 2.81) in a previous multivariate analysis from a single institution [117] as well as PSA level < 10 ng/ml (HR: 0.47) [118].

d.4.2 Interventions to prevent radiation induced urethral strictures

Delaying adjuvant or salvage EBRT by nine months is associated with lower rates of urethral stricture (HR: 0.6) [119]. This has to be balanced with risk of delaying treatment in terms of cancer control [79]. In BT, it has been reported that downward movement of needle applicators occurs between fractions [120]. This may explain why strictures occur below the prostatic apex [118] in the so called "hot spot" [121]. Several measures taken together are thought to have contributed to a reduction in urethral stricture formation with BT including reduction of dose to the "hot spot", more careful needle placement, avoiding midline insertion and the introduction of plastic needles rather than steel [114].

e. Failed hypospadias repair.

Although urethral strictures after hypospadias repair are sometimes considered as iatrogenic [38], they are a very specific subtype and should be considered as a separate entity. The main reasons for this are the absence of spongiosus tissue at different levels within the penile urethral segment, and the lack of high-quality local tissues for urethral reconstruction [122].

f. Congenital

The diagnosis of a congenital urethral stricture can only be made in the absence of other possible aetiology, such as iatrogenic, inflammatory, and traumatic causes [25]. Congenital strictures are thought to be consequent to incomplete or incorrect fusion of the urethra formed from the urogenital sinus with the urethra formed following closure of the urethral folds. They typically have a deep bulbar location and are usually short. In general, congenital strictures are diagnosed at a young age (Moorman's ring or Cobb's collar).

g. Idiopathic

Idiopathic strictures are seen in 34% of all penile strictures and in 63% of all bulbar strictures [123]. Unrecognised trauma is thought to be a possible aetiology of idiopathic urethral strictures [27].

3.3.2 ***Aetiology in females***

The cause of FUS was idiopathic in 48.5%, iatrogenic in 24.1%, resulting from prior urethral dilations, difficult/traumatic catheterisation with subsequent fibrosis, urethral surgeries (mainly diverticulum surgery, fistula repair and anti-incontinence procedures) and trauma (mainly following pelvic fracture) in 16.4% [124-136]. Radiation therapy and infections are rare causes of FUS [137]. The most common segment of urethra affected is the mid- or mid-to-distal (58%). Panurethral strictures are rare (4%) [15, 124, 126, 127, 129-131, 136, 138].

For further information see online supplementary Tables S3.1 and S3.2.

4. CLASSIFICATIONS

4.1 According to stricture location

Classification according to stricture location is important as this will affect further management.

4.1.1 ***In males***

4.1.1.1 Anterior urethra

The anterior urethra runs from the meatus to the urogenital diaphragm and is surrounded in its entire length by the corpus spongiosum [11, 139]. Further subdivision is made in three different areas (from distal to proximal) [12]:

Meatal strictures: these strictures are located at the external urethral meatus and may extend into the fossa navicularis of the glans.

Penile strictures: these are located in the segment between the fossa navicularis and the bulbar urethra. Externally, the penile urethra begins approximately at the balanopreputial sulcus and continues to the penoscrotal junction. The whole penile urethral segment lies in the groove ventral to corpora cavernosa and is surrounded by a thin layer of corpus spongiosum.

Bulbar strictures: the bulbar urethra starts at the penoscrotal junction and is surrounded by the bulbospongious muscle. It ends in the membranous urethra proximally at the level of the urogenital diaphragm. The bulbar urethra can be subdivided into a proximal and distal part. The proximal bulbar urethra is defined as the segment within 5 cm of the membranous urethra; the urethra lies eccentrically in this part with abundant ventral spongious tissue. The distal bulbar urethra is defined as the adjoining segment extending to the penoscrotal junction [140]. Strictures extending towards the membranous urethra are termed bulbomembranous strictures (BMS).

Penobulbar strictures: these extend from the penile urethra into the bulbar segment, compromising long segments of urethra.

The difference between penobulbar strictures and multifocal strictures should be noted. The latter are defined by two or more narrowed segments, either in the same or different subdivision of the urethra but preserving healthy lengths of urethra between them (e.g., iatrogenic strictures related to TUR procedures which typically affect the fossa navicularis and the penoscrotal junction with healthy urethra in between).

4.1.1.2 Posterior urethra

The posterior urethra is approximately 5 cm long, with three different segments [12]:

- The membranous urethra is the area of the urethra traversing the urogenital diaphragm, between the proximal bulbar and the distal verumontanum.

- The prostatic urethra runs through the prostatic gland, starting at the proximal membranous urethra and extending to the bladder neck.
- The bladder neck is surrounded by the internal urinary sphincter and is the junction between the prostatic urethra and the bladder. Stenosis (or contracture) of the bladder neck implies a prostate *in situ* (i.e., after TURP or simple prostatectomies). If the narrowing or obliteration appears at this level but after a RP, the correct term is VUAS [12].

*4.1.2 **In females***

The female urethra is approximately 4 cm long and arbitrarily divided in an upper, mid, and lower part [15, 124, 126, 127, 129-131, 136, 138].

4.2 According to stricture tightness

The definition of low- vs. high-grade strictures remains debatable [141-143]. A urethral plate less than 3 mm is considered a high-grade or tight stricture [144]. It has been demonstrated with a normally functioning bladder that flow rate will not diminish until the urethral lumen has a diameter below 10 Fr [142].

Table 4.1 presents a suggested classification for male patients with a normal functioning bladder. This classification was developed by the EAU Urethral Stricture Panel based on a consensus process.

Table 4.1: EAU classification according to the degree of urethral narrowing

Category	Description	Urethral lumen (French [Fr])	Degree
0	Normal urethra on imaging	-	-
1	Subclinical strictures	Urethral narrowing but ≥ 16 Fr	Low
2	Low grade strictures	11-15 Fr	
3	High grade or flow significant strictures	4-10 Fr	High
4	Nearly obliterative strictures	1-3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

4.3 Strictures in transgender men and woman

*4.3.1 **Trans women***

After MtF gender confirming surgery, the penile urethra has been resected. Meatal strictures are defined as strictures occurring at the neomeatus, which is formed between the junction of the distal bulbar urethra and the neovagina. The other segments (bulbar and posterior) are the same as in a biological man.

*4.3.2 **Trans men***

Four different areas can be identified in the urethra after FtM gender confirming surgeries [145]:

- The native urethra is the female urethral segment which remains preserved during surgery. It goes from
- the bladder neck to the original external meatus.
- The fixed part (pars fixa) or perineal urethra follows the native urethra, starting at the original external
- meatus. This segment is reconstructed using local tissues, typically vestibular mucosa, or anterior vaginal mucosa. Its course is similar to the bulbar urethral segment in males, but without being covered by spongiosal tissue.
- The anastomotic part is the area where the pars fixa joins the neophallus.
- The phallic urethra is the segment located within the neophallus or the metoidioplasty and is usually made of skin tube. Its course is similar to the penile urethra in males, but without being covered by spongiosal tissue.

5. DIAGNOSTIC EVALUATION

A comprehensive diagnostic evaluation of urethral stricture disease encompasses clinical history and examination, urinalysis (+/- culture), uroflowmetry and post-void residual (PVR) assessment, radiography, and endoscopy.

5.1 Patient history

The purpose of history taking is to assess symptoms including severity and duration, possible aetiology, prior treatments, complications, associated problems, and patient factors that may impact upon surgical outcome.

The clinical presentation of urethral stricture disease is varied. In a retrospective analysis of 611 patients with an endoscopically confirmed diagnosis of urethral stricture, LUTS were the most common presentation (54.3%) followed by acute urinary retention (22.3%), urinary tract infection (UTI) (6.1%) and difficult catheterisation (4.8%) [146]. In a retrospective study of 214 patients who underwent anterior urethroplasty, weak stream was reported as the most common individual LUTS (49%) followed by incomplete emptying (27%) and urinary frequency (20%) [147]. A further retrospective series of 614 patients undergoing anterior urethroplasty found post-void dribble to be present in 73% [148].

Genitourinary pain is a common feature, affecting 22.9-71% [34, 146]. Pain may be felt in the bladder and/or urethra, is associated with more severe LUTS, is more likely to be felt by younger men and resolves in most following reconstruction [34]. Other complaints include spraying (9%), visible haematuria (3.1-5%), urethral abscess/necrotising fasciitis (2.3%), urgency (14%) and incontinence (1-4%) [146, 147].

To establish aetiology, an enquiry about a history of pelvic, genital, or perineal trauma, prior instrumentation, prior surgeries, irradiation or focal therapies and urethritis should be made. It is important to document prior surgical approaches and date of the most recent intervention (e.g., dilatation) as this may impact upon the timing of radiological evaluation or surgical treatment.

Problems of sexual function are common in patients with urethral stricture disease [149, 150] and sexual function may be impacted upon by surgical intervention [151, 152]; therefore, the status of erectile and ejaculatory function should be established and documented using validated tools.

The performance status of the patient should be determined as it may influence the choice of treatment (curative or palliative). A past medical history should assess for factors that may impact upon tissue healing including diabetes, immunosuppression, and smoking. Oral tobacco use or the chewing of betel leaves may increase the risk of morbidity at the harvest site or render oral mucosa too poor for use. Prior harvest of oral mucosa should be noted as alternative sources for tissue transfer may need to be considered [153] or alternative surgical approaches (e.g., perineal urethrostomy [PU]).

5.2 Physical examination

The abdomen should be examined for the presence of a palpable bladder. The location of any suprapubic tube should be noted to assess its potential utility for antegrade cystoscopy or the placement of a sound (to facilitate repair) [154]. Examination of the genitalia should note the presence of foreskin, the position and size of the meatus as well as any evidence of scarring suggestive of LS. Pre-operative biopsy to confirm LS may be performed if this alters management and is essential if malignancy is suspected [155].

The presence of penile or perineal fistulae should be noted. The urethra should be palpated to assess for induration suggestive of significant fibrosis. Rarely a mass may signify a urethral carcinoma. A rectal examination to assess for prostatic pathology, which may be the cause of urinary symptoms, should be undertaken. In patients with posterior urethral stenosis rectal adherence to the prostate and the mobility of the surrounding tissues should be assessed [156]. The oral cavity should be examined for the suitability of oral mucosa. Measurement of BMI will identify obese individuals who are at greater risk of leg compartment syndrome when placed in the lithotomy position for a prolonged time period [157]. Assessing hip mobility is important when considering an exaggerated lithotomy position as some patients may have limited hip flexion due to unresolved orthopaedic problems [154].

*5.2.1 **Further diagnostic evaluation***

5.2.1.1 Patient reported outcome measure (PROM)

The first validated urethral stricture surgery PROM (USS-PROM) was reported in 2011 [158]. It consists of six LUTS questions derived from the International Consultation on Incontinence Questionnaire Male LUTS (ICIQ-MLUTS) module, a LUTS-specific QoL question, the Peeling voiding chart and the EQ-5D to assess overall health-related QoL (HRQoL). The post-operative questionnaire contains an additional two questions to assess overall patient satisfaction. This PROM has been validated in several other languages (German, Spanish, Italian, Dutch, Turkish, Polish, Japanese) and is increasingly used in research studies as well as clinical practice. A further PROM is in development in North America but requires validation [159] (see section 11. Follow-up).

Summary of evidence	LE
A specific urethral stricture surgery patient reported outcome measure was found to have psychometric validity in the assessment of patient-derived benefit from surgical intervention for urethral stricture disease.	2a
Sexual dysfunction is prevalent in patients with urethral strictures and sexual function can be affected by surgical management of urethral stricture.	3

Recommendations	Strength rating
Use a validated patient reported outcome measure to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease.	Strong
Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease.	Strong

5.2.1.2 Urinalysis and urine culture

Urinalysis is an essential component of the work up of patients with LUTS. If infection is suggested, urine culture should be performed to confirm the diagnosis and identify the causative organism and sensitivity to antibiotics. Bacteriuria should be treated prior to surgical intervention to prevent peri-operative sepsis [160] (see section 10. Peri-operative care).

5.2.1.3 Uroflowmetry and post-void residual estimation

A reduced maximum flow rate with a prolonged plateau is characteristic of the constrictive obstruction caused by urethral stricture. However, interpretation of flow patterns is subjective and is not considered a reliable screening tool for the detection of stricture [161]. To overcome this, a statistical model based on uroflowmetry parameters was developed and was found to predict urethral stricture with a sensitivity of 80–81% and a specificity of 77–78% [161]. Uroflowmetry is usually combined with ultrasound (US) estimation of PVR to identify patients with urinary retention who may require emergent bladder drainage. Uroflowmetry parameters can also be used for monitoring patients and in the assessment of treatment response (see section 11. Follow-up).

Urodynamic studies are not indicated in the vast majority of patients with urethral stricture disease. In patients with suspected bladder dysfunction (e.g., severe storage LUTS, history of irradiation or neurological disease), an assessment of bladder function may help surgical decision making and patient counselling. Similarly, when there is concern that flow impairment or increased PVR are due to detrusor underactivity or an acontractile detrusor, a urodynamic study may help predict the likelihood that the patient would need to perform intermittent self-catheterisation (ISC) post-operatively. The only urodynamic parameter found to distinguish a diagnosis of urethral stricture from BPO is urethral closure pressure which is lower in the former due to the constrictive nature of the obstruction (22.07 vs. 28.4 cm H_2O, p=0.0039, r=0.61, BPO vs. stricture) [162].

Summary of evidence	LE
Uroflowmetry pattern interpretation by use of a statistical model was found to be predictive of urethral stricture disease.	3

Recommendation	Strength rating
Perform uroflowmetry and estimation of post-void residual in patients with suspected urethral stricture disease.	Strong

5.2.1.4 Urethrography

Retrograde urethrography (RUG) has widely been used as the investigation of choice for evaluating the stricture presence, location, length, and any associated anomalies (e.g., false passages, diverticula) [163].

The reported sensitivity and specificity of RUG in the diagnosis of strictures is 91% and 72%, respectively [164]. The positive predictive value (PPV) was 89% and the negative predictive value (NPV) was 76% [164]. Most reports suggest that RUG underestimates stricture length [165, 166]. Interpretation of RUG findings by urologists were found to be more accurate at predicting urethral stricture location and length as compared to evaluation by an independent physician [167].

Limitations of RUG include difficulty assessing very distal strictures and assessing the proximal extent of strictures which are too narrow to permit passage of adequate contrast. Combining a RUG with voiding

cystourethrography (VCUG) can allow adequate visualisation of the urethra proximal to the stricture and a more accurate assessment of stricture length in (nearly) obliterative strictures, stenoses and gap in pelvic fracture urethral injury (PFUI) [168, 169]. In addition, urethrography provides only a two-dimensional assessment of stricture and the results may be affected by the amount of penile stretch [170], degree of pelvic rotation and patient body habitus [171]. Risks of the procedure include infection, discomfort [162], contrast reaction from intravasation of contrast [172] in addition to the risk of radiation exposure. Urethrographic clamp devices (Brodny, Knutson) are available and were found to be less painful than using the Foley catheter technique [173].

Summary of evidence	LE
Retrograde urethrography is a widely available and easy to perform method of diagnosing and assessing urethral stricture but may underestimate stricture length.	2a
Retrograde urethrography alone is not able to assess stricture length (or gap) in obliterative strictures or stenosis.	2a
Urethrographic clamp devices are less painful than using the Foley catheter technique.	2a

Recommendations	Strength rating
Perform retrograde urethrography (RUG) to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery.	Strong
Combine RUG with voiding cystourethrography to assess (nearly)-obliterative strictures, stenoses and pelvic fracture urethral injuries.	Strong
Use clamp devices in preference to the Foley catheter technique for urethrographic evaluation to reduce pain.	Weak

5.2.1.5 Cystourethroscopy

Cystourethroscopy allows for accurate visual detection of a suspected stricture or can rule out a stricture as cause of obstructive voiding [164]. It can detect narrowing of the urethral lumen before changes in uroflowmetry and symptoms [143]. Cystourethroscopy can also assess the presence of LS or other pathology but cannot usually assess stricture length as the calibre of most cystoscopes is greater than most symptomatic strictures [174]. To overcome this, use of smaller calibre ureteroscopes (6.5 Fr and 4.5 Fr) has been reported [174]. This also allows an assessment of the bladder prior to surgery and may identify other pathology such as bladder stones. Cystourethroscopy is particularly helpful for diagnosing proximal BMS which may be missed on RUG [175].

Retrograde urethroscopy combined with antegrade cystoscopy via the suprapubic tract may be used to evaluate PFUI and plan the surgical approach. It allows an assessment of the length of the defect, the competence of the bladder neck, the involvement of the bladder neck in scarring in addition to identifying the presence of bony spicules or other abnormalities (e.g., fistulae, stones) [176]. Combined retrograde and antegrade cystoscopy was found to provide similar estimates of length of urethral defect in patients with PFUI as combined retrograde and antegrade cystourethrography, but was more likely to detect fistulae, false passages, and calculi [176].

Summary of evidence	LE
Cystourethroscopy will reliably detect the presence of a urethral stricture.	3
Combined retrograde urethroscopy and antegrade cystoscopy is more accurate than retrograde and voiding cystourethrography at identifying associated abnormalities such as fistulae, false passages, and calculi in patients with PFUI.	3

Recommendations	Strength rating
Perform cystourethroscopy as an adjunct to imaging if further information is required.	Weak
Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required.	Weak

5.2.1.6 Ultrasound

Ultrasound of the urethra or sonourethrography (SUG) provides a non-invasive three-dimensional assessment of anterior urethral stricture disease; including stricture location, length, and the degree of associated spongiofibrosis [177].

Several studies have compared SUG to RUG and cystoscopic or intraoperative findings. Sonourethrograpy was found to be more accurate at diagnosing stricture presence compared to RUG [173, 178]. Sonourethrography was also found to more accurately estimate stricture length (94% correlation with intraoperative findings) than RUG (59% correlation with intraoperative findings) ($p < 0.001$) [166]. A further study showed similar findings and found that the closest correlation for stricture length at operation was for strictures in the penile urethra [165]. Intraoperative sonourethrogram findings have also been found to change the planned reconstructive approach (based on pre-operative retrograde urethrogram) in 19% of men undergoing anterior urethral reconstruction [171]. Sonourethrography incorporating real-time elastography can provide a qualitative and quantitative assessment of spongiofibrosis [179, 180]. The clinical relevance of assessing the degree of spongiofibrosis pre-operatively remains to be established. Three-dimensional reconstruction of sonographic images is investigational at present [181].

The advantages of SUG are that it can be performed in the outpatient setting, provides information on the degree of spongiofibrosis and its relatively low cost [177]. Limitations of the technique include lower sensitivity for detection of strictures in the bulbar urethra, operator dependency, and the need for urethral distension requiring intraurethral anaesthesia. Sonourethrography requires specialised training in the use of US and is currently not in widespread usage.

Table 5.1: Diagnostic accuracy of sonourethrography compared to other modalities and surgical findings

Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Berne-Mestre *et al*. 2018 [173]	113	Anterior and posterior	RUG, VCUG, surgical findings	SUG more accurate than RUG ($p < 0.05$)	-	-
Ravikumar *et al*. 2014 [178]	40	Anterior and posterior	RUG, VCUG, surgical findings	Anterior: SUG 100% sensitivity, 100% specificity Posterior: SUG 75% sensitivity, 50% specificity.	-	-
Kalabhavi *et al*. 2018 [166]	30	Anterior	RUG, surgical findings	-	-	-
Krukowski *et al*. 2018 [165]	66	Anterior	RUG, surgical findings	-	-	-

N = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

5.2.1.7 Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used to image PFUIs, posterior urethral stenoses and anterior urethral strictures.

Several studies have compared MRI urethrogram to RUG and intraoperative findings. Magnetic resonance imaging urethrogram was found to be as accurate as RUG at detecting stricture site in anterior urethral strictures [182]. In terms of stricture length both MRI urethrogram and RUG reliably correlated with intraoperative findings [182]. On the other hand, a further study of patients with anterior urethral strictures found MRI urethrogram stricture length to correlate more closely with surgical findings than RUG [183].

In a mixed group of anterior urethral strictures and posterior urethral stenoses, MRI urethrogram was as accurate (sensitivity = 100%, specificity = 91.7%) as combined RUG and sonourethrography (sensitivity = 100%, specificity = 91.7%) at diagnosing strictures [184]. There was no significant difference in the measurement of stricture length [184]. In a further study of patients with posterior urethral stenosis, MRI estimation of stenosis length correlated more closely with operative findings compared to RUG [185]. In patients with PFUI, MRI measurement of pubo-urethral stump angle (angle between long axis of pubis and line between the distal end of the proximal urethral stump and lower border of inferior pubic ramus) was predictive of an elaborated approach on multivariate analysis [186].

Magnetic resonance imaging was also found to be more accurate at diagnosing associated pathologies e.g., diverticula, tumours, fistulae, and stones [184]. In cases of fistulation between the urinary tract and pubic symphysis after irradiation for prostate cancer, the fistula tract can be clearly demonstrated on MRI [187]. Other imaging modalities, including computed tomography (CT), may fail to identify the tract and the problem may be misdiagnosed as isolated osteomyelitis of the pubic bone leading to medical management with antibiotics rather than surgical excision [187].

The main advantage of MRI is greater anatomical detail, which is countered by the expense of the procedure and the greater complexity in interpreting images. The technique is not commonly used for routine situations, but it may be helpful in diagnosing associated pathologies which may alter patient management.

Table 5.2: Diagnostic accuracy of MRI compared to other modalities and surgical findings

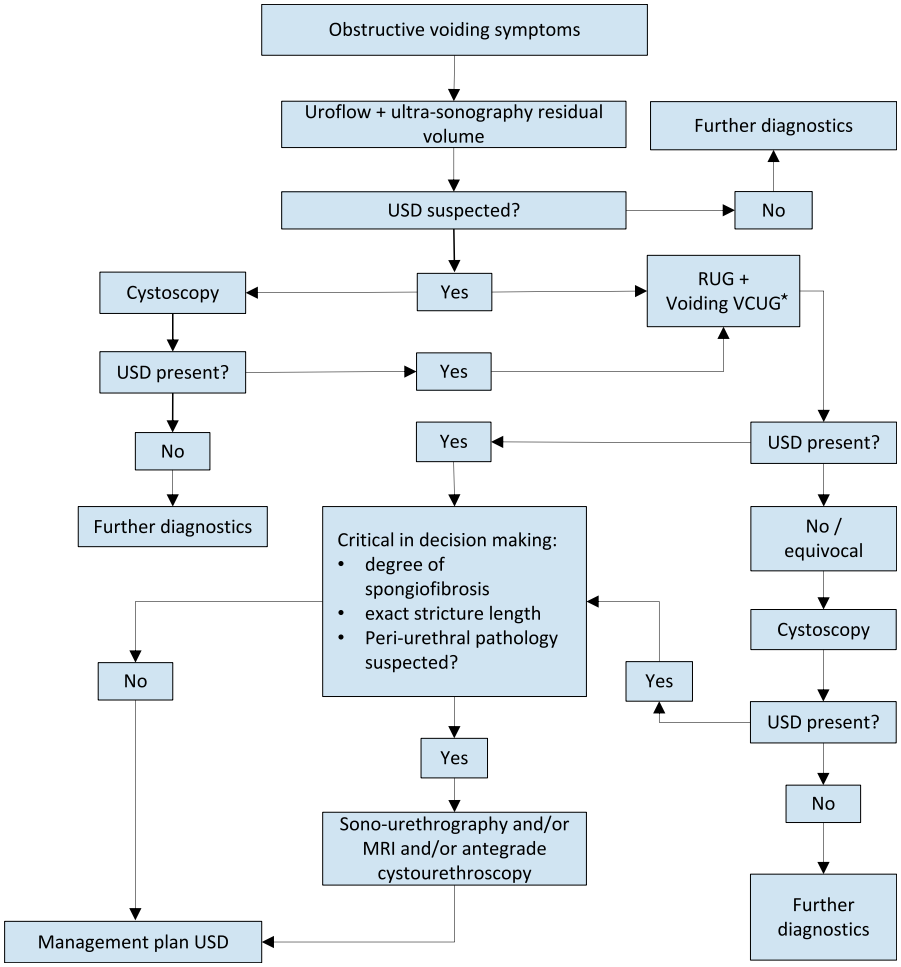
Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Murugesan *et al*. 2018 [182]	32	Anterior	RUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 100% specificity)	-	-
Fath El-Bab *et al*. 2015 [183]	20	Anterior	RUG, Surgical findings	-	-	MRI more accurate than RUG.
El-Ghar *et al*. 2010 [184]	30	Anterior and posterior	RUG + SUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 91.7% specificity)	-	MRI and RUG equivalent.
Oh *et al*. 2010 [185]	25	Posterior	RUG + SUG, Surgical findings	-	-	MRI more accurate than RUG + VCUG.

MRI = magnetic resonance imaging; n = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

Summary of evidence	LE
Magnetic resonance imaging is more accurate than retrograde urethrography and voiding cystourethrography at determining length of posterior urethral stenoses and can detect alternative associated pathologies e.g., diverticula, fistulae.	2a

Recommendation	Strength rating
Consider magnetic resonance imaging urethrography as an ancillary test in posterior urethral stenosis.	Strong

Figure 5.1: Diagnostic flowchart of patients with suspected urethral stricture disease



**Use VCUG in case of (nearly-) obliterative strictures or stenosis.*
MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cystourethrogram.

6. DISEASE MANAGEMENT IN MALES

6.1 Conservative options

6.1.1 ***Observation***

A stricture will usually result in diminution in flow once the calibre of the urethral lumen is ≤ 10 Fr [142]. In other strictures (> 10 Fr), the diagnosis is often made by coincidence in asymptomatic patients because of a urologic examination for other reasons (e.g., cystoscopy, need for urethral catheterisation) [142]. Purohit et al., performed observation and repeated cystoscopic evaluation of 42 subclinical, incidentally encountered strictures (≥ 16 Fr). After a median follow-up of 23 months, only five (12%) strictures progressed to a low-grade stricture (11-15 Fr). No patient developed symptoms and none of them needed surgical intervention [142]. These patients are candidates for observation although no evidence exist on the long-term evolution of these strictures.

In a series of anatomic stricture recurrence (≤ 16 Fr) after urethroplasty, only 65% of patients were symptomatic [143]. Some asymptomatic patients refused further intervention because they had experienced substantial improvement after their primary urethroplasty. These patients were considered as functional “success” [143]. A multicentric study of the Trauma and Urologic Reconstructive Network of Surgeons observed an important discrepancy between cystoscopic recurrence and need for further intervention [141]. Patients with a large calibre (> 16 Fr) recurrence had a one and two-year need for intervention rate of 4% and 12%, respectively. Of note, patients with small-calibre (≤ 16 Fr) recurrence had a one and two-year need for intervention rate of only 41% and 49%. Patients who needed intervention had poorer PROMs suggesting clinical symptoms and

bother. There is no information on long-term complications in patients with recurrences who did not undergo intervention. In cases of an asymptomatic stricture recurrence, it might be an option not to intervene but to perform regular follow-up.

Care must be taken about the term "asymptomatic" stricture (recurrence) as patients might conceal their bother and symptoms by different means (not drinking, social avoidance) and might only search for medical help once concealment is no longer tenable [188].

*6.1.2 **Suprapubic catheter***

Radiation-induced urethral strictures are a difficult to treat population as stricture-free rates for urethral reconstruction are lower compared to those in non-irradiated patients [189]. Fuchs *et al.*, evaluated 75 patients who were initially treated by suprapubic diversion for radiation-induced isolated BMS [190]. Only 51% eventually decided to undergo urethroplasty after a mean follow-up period of 25 months. Although there was no significant difference in overall performance status between patients with a chronic suprapubic catheter vs. those undergoing urethroplasty, all patients with a poor performance score remained with a suprapubic catheter. Patients with concomitant stress urinary incontinence (SUI) opted more often to keep their suprapubic catheter as the SUI improved in 61% of cases. On the other hand, patients who kept their suprapubic catheter suffered from catheter-related complications in 27% of cases. Urinary diversion by ileal conduit was performed in 30% of patients who remained with a suprapubic catheter while this was only the case in 8% who underwent urethroplasty.

A suprapubic catheter is also an option in frail patients not able to undergo surgery or in patients who do not want (further) urethral surgery and are willing to accept the complications of a suprapubic catheter [191].

Summary of evidence	**LE**
Patients with asymptomatic incidental (> 16 Fr) strictures have a low risk of progression and to develop symptoms.	3
Only half of the patients initially treated with a suprapubic catheter for radiation-induced bulbomembranous strictures will proceed with urethroplasty.	3

Recommendations	**Strength rating**
Do not intervene in patients with asymptomatic incidental (> 16 Fr) strictures.	Weak
Consider long-term suprapubic catheter in patients with radiation-induced bulbomembranous strictures and/or poor performance status.	Weak

6.2 Endoluminal treatment of anterior urethral strictures in males

The ability to treat the majority of strictures by less invasive and time-consuming means, offers obvious benefits particularly when specialist surgical services are not available, or patients simply prefer a more pragmatic immediately available solution.

*6.2.1 **Direct vision internal urethrotomy***

In contemporary practice, direct vision internal urethrotomy (DVIU) is commonly performed as a first-line treatment of urethral strictures [192]. It is usually performed under general or spinal anaesthesia in well-resourced countries but shown to be well tolerated under local anaesthesia with or without sedation [193-195].

6.2.1.1 Indications of "cold knife" direct vision internal urethrotomy

6.2.1.1.1 Direct vision internal urethrotomy for primary stricture treatment

In the only high-level evidence study, Steenkamp *et al.*, randomised 210 patients with seemingly comparable non-obliterative strictures at all locations of the urethra to either filiform dilatation vs. DVIU with local anaesthesia on an outpatient basis [196]. They collected objective data with RUG performed at seven follow-up visits (3, 6, 9, 12, 24, 36 and 48 months). This unique study showed that urethral dilatation is equally effective as DVIU but both procedure modalities become less effective with increasing stricture length (see section 6.2.1.1.3.1).

A Cochrane review in 2012 could not identify a single prospective RCT comparing DVIU (or dilatation) with urethroplasty at the anterior urethra [197]. Since then, the randomised Open-label Superiority Trial of Open Urethroplasty vs. Endoscopic Urethrotomy (OPEN) prospectively randomised patients with a recurrent bulbar stricture between open urethroplasty and DVIU but this was for recurrent bulbar strictures only and not as primary treatment [198] (see section 6.2.1.1.2). A retrospective cohort series in boys with bulbar stricture reported a patency rate of 53% for DVIU and 80% for urethroplasty. No statistical analysis was performed and no information on stricture length was available in both cohorts which makes direct comparison hazardous [199].

Patency rates vary considerably between 8% and 77% after DVIU (predominantly without prior urethroplasty) in retrospective cohort studies with minimum follow-up of one year [69, 199-208] (Table 6.1). Median time to recurrence was less than twelve months in most series [69, 200-202, 204-206]. This large variation in patency rate can be in part explained by the heterogeneous nature of the strictures and various definitions of patency used by the authors in these series. Indication to perform DVIU is dependent on various stricture characteristics that are prognostic for a successful outcome.

Table 6.1: Results of DVIU in series with minimum follow-up > 12 months

Study	N	Age (years)	Follow-up (months)	Location	Length (cm)	Previous interventions	TTR (months)	Patency rate (%)
Santucci *et al*. [200]	76	53 (range: 17-100)	18 (range: 1-30)	Bulbar: 37 (49%) Penile: 4 (5%) Penobulbar: 1 (1%) Unknown: 34 (45%)	1.5 (0.2-5)	Primary: 100%	7	8
Pansadoro *et al*. [201]	224	62 (range: 11-90)	98 (range: 60-216)	Bulbar: 142 (63%) Penile: 37 (17%) Penobulbar: 45 (20%)	1.6 (0.1-6.5)	Primary: 88% Recurrent: 12%	< 12 56% -	32 -
Al Taweel *et al*. [204]	301	37 (range: 17-82)	36	Bulbar: 227 (75%) Penile: 50 (17%) Penobulbar: 24 (8%)	1.3 (0.4-4.2)	Primary: 47% Recurrent: 53%	10 -	8.3 -
Barbagli *et al*. [203]	136	37 (IQR: 25-48)	55 (range: 36-92)	Bulbar: 100%	1-2 cm: 45% 2-3 cm: 40% 3-4 cm: 15%	Primary: 100%	25	57
Kluth *et al*. [202]	128	64 (SD: 16)	16 (IQR:6-43)	Penile: 15 (12) Bulbar: 112 (88) Unknown: 1 (1%)	NR	Primary: 66% Recurrent: 34%	8 -	52 -
Pal *et al*. [205]	186	39 (SD:15)	1st DVIU: 58 (SD: 15) 2nd DVIU: 56 (SD: 15) 3rd DVIU: 45 (SD: 15)	bulbar: 100%	NR	Primary: 69% Repeat: 31%	8.5 -	1st DVIU: 30 2nd DVIU: 23 3rd DVIU: 13
Diamond *et al*. [199]	53	14	30 (range: 6-64)	bulbar: 100%	NR	Primary: 100%	23	53%
Launonen *et al*. [206]	34	6 (range: 0-16)	79 (range: 7-209)	Bulbar: 74% Penile: 21% Penobubar: 6%	≤ 2 cm: 85% > 2 cm: 15% -	Primary: 100%	4	26%
Redon-Galvez *et al*. [207]	67	57 (range: 15-91)	40 (range: 12-120)	Penile:9% Bulbar: 64% VUA: 21% Membranous: 6%	≤ 1 cm: 82% > 1 cm: 18%	Primary: 90% Repeat: 10%	< 24 -	63% -
Harraz *et al*. [208]	430	50 (SD: 15)	29 (range: 3-132)	Bulbar: 100%	< 2 cm	NR, prior urethroplasty excluded	NR	58%
Yürük *et al*. [69]	193	65 (SD: 13)	36 (SD: 12)	Bulbar: 100%	< 1 cm: 140 (73%) 1-2 cm: 21 (11%) 2-3 cm: 32 (17%)	0%	87% of recurrence ≤ 3 100% of recurrence ≤ 6	77% -

DVIU = Direct vision internal urethrotomy; IQR = interquartile range; N = number of patients; NR = not reported SD = standard deviation; TTR = time to recurrence.

6.2.1.1.2 Direct vision internal urethrotomy for recurrent strictures and as salvage treatment after failed urethroplasty

In the OPEN trial, a recurrent stricture was defined as at least one previous failed intervention (endoscopic urethrotomy, urethral dilatation, urethroplasty) [209]. The previous intervention was predominantly DVIU. Despite poor recruitment, 108 and 112 patients were randomised to urethroplasty and DVIU respectively in a 24-month study protocol. Both groups had a similar improvement in voiding score symptoms after intervention. However, patients undergoing urethroplasty had 2.6 higher odds of experiencing an improvement of ≥ 10 ml/s in their maximum urinary flow compared to those undergoing urethrotomy (p=0.001) [209]. Need for re-intervention was observed in 13.8% vs. 25.9% of cases respectively allocated to urethroplasty and DVIU resulting in a 48% lower risk for re-intervention with urethroplasty (HR: 0.52; 95% CI: 0.31-0.89; p=0.017) [209]. Of note, self-dilatation was not considered a re-intervention [209]. Direct vision internal urethrotomy is also used as salvage treatment for recurrent strictures after urethroplasty. Brown *et al*., used DVIU for stricture recurrence (mean length: 4 cm; range: 1.5-7 cm) after excision and primary anastomosis (EPA), buccal mucosa grafts (BMG) urethroplasty and penile skin graft urethroplasty [210]. Patency was obtained in thirteen out of 37 cases (35%) after a single DVIU. After free graft urethroplasty (FGU), a short, veil-like stricture (or "diaphragm") might develop at the distal or proximal end of the graft. Rosenbaum *et al*., used DVIU to a selected cohort of 43 patients with a short (< 1 cm), veil-like stricture after BMG urethroplasty [211]. After a mean follow-up of twelve months, patency rate was 51%. Farrell *et al*., performed DVIU with mitomycin C (MMC) injection in seventeen patients with a short (median 2 cm; interquartile range [IQR] 1-2.5 cm) recurrence after bulbar urethroplasty (no details on technique available) and patency was achieved in twelve (71%) patients [212].

6.2.1.1.3 Predictors of failure of "cold knife" direct vision internal urethrotomy

Several groups tried to identify prognostic factors to predict which patients are most likely to fail initial treatment (Table 6.2).

6.2.1.1.3.1 Stricture length

Stricture length was identified as an important predictive factor for recurrence in several series. For bulbar strictures, Pansadoro *et al*., found a 71% and 18% patency rate for < 1 cm and ≥ 1 cm strictures respectively (p < 0.001) [201]. In the series of Al Taweel *et al*., no patient with a stricture > 1 cm who achieved patency was stricture-free, whereas this was 27% for strictures < 1 cm (p < 0.001) [204]. Barbagli *et al*., reported an estimated five-year patency rate of 71%, 51% and 39% for 1–2 cm, 2–3 cm and 3–4 cm strictures respectively (p < 0.00001) [203]. Pal *et al*., reported no patency in case of strictures > 1 cm [205]. In their prospective study, Steenkamp *et al*., reported that for each 1 cm increase in the length of the stricture the risk of recurrence was increased by 1.22 (95% CI: 1.05-1.43) [196]. In a paediatric series, a 0% patency rate was obtained for strictures > 2 cm [206]. Redon-Galvez *et al*., reported a 25% patency rate for strictures > 1 cm, whereas strictures ≤ 1 cm had a 71% patency rate (p=0.006). This difference remained statistically significant in the multivariable analysis, when adjusted for stricture location (HR: 1.75; p=0.025) [207]. A SR of case series calculated a weighted average patency rate of 71.2% vs. 23.2% for strictures less and more than 1 cm respectively (p < 0.0001) [213].

6.2.1.1.3.2 Stricture tightness (calibre)

Pansadoro *et al*., reported a patency rate of 69% and 34% for strictures more than and less than 15 Fr in calibre, respectively (p < 0.001) [201]. Using pre-operative maximum urinary flow (pQ_{max}), as surrogate for urethral calibre, Barbagli *et al.,* stratified patients into three groups (pQ_{max} < 5 vs. 5–8 vs. > 8 ml/s) and reported an estimated five-year patency rate of 31% vs. 53% vs. 83%, respectively (p < 0.00001) and the importance of pQ_{max} was confirmed in multi-variate analysis [198]. Kluth *et al*., could not confirm the significance of pQ_{max} on the outcome of DVIU [202].

6.2.1.1.3.3 Number of strictures

Pansodoro *et al*., found poorer patency rates in case of DVIU for multiple strictures compared to a single stricture at both the bulbar (18% vs. 50%; p < 0.001) and penile urethra (8% vs. 35%; p=0.013) [201]. Pal *et al*., reported a 0% patency rate in case of multiple strictures whereas this was 35% for a single stricture (p=0.03) [205].

6.2.1.1.3.4 Stricture aetiology

Harraz *et al*., identified idiopathic stricture aetiology as an independent risk factor for failure (HR: 3.11; p=0.035) [208]. On the other hand, stricture aetiology was not a predictive factor in many other series [201, 205, 206].

6.2.1.1.3.5 Stricture location

Several series have reported a better patency rate for bulbar strictures compared to penile stricture or penobulbar strictures [196, 201, 204]. Kluth *et al*., could not identify stricture location as an independent prognostic factor but only 12% of patients had a stricture at the penile urethra [202].

6.2.1.1.3.6 Previous interventions

Pansodoro *et al*., [201], Al Taweel *et al*., [204] and Heyns *et al*., [214] found a 0% patency rate after two or more prior failed DVIU, whereas this occurred after three and four prior failed DVIUs in the series of Santucci *et al*., [200] and Launonen *et al*., [206], respectively. Kluth *et al*., identified secondary DVIU for a recurrent stricture as an independent risk factor for stricture recurrence (HR=1.78; 95% CI: 1.05-3.03; p=0.032) [202]. Pal *et al*., found significantly better patency rates after a 1st DVIU compared to a 2nd or 3rd DVIU [205].

6.2.1.1.3.7 Other factors

Two series could not identify age, diabetes, hypertension, obesity and smoking as independent predictive factors [202, 203]. However, Harraz *et al*., identified that older age at presentation and obesity are independent predictors of failure after DVIU [208].

In the absence of well-designed, adequately powered multi-centre trials it is difficult to answer the question as to which clinical factors are predictive of failure of DVIU in men with urethral strictures. However, based on the predictors evaluated above and further supported by consensus papers [215-217], one can summarise that the best candidates are previously untreated patients with a single, short (max. 2 cm) bulbar stricture. In a selected group of patients (n=60), a patency rate of 77% was reported for a single, short, primary bulbar stricture with a minimum follow-up of five years [201]. This is confirmed by a more contemporary cohort of patients with untreated short (1-2 cm) bulbar urethral strictures, in which the estimated five-year patency rate was 71% [203].

Table 6.2: Predictors for urethral patency after direct vision internal urethrotomy

Author	Location	Length	Calibre	Multiplicity	Prior DVIU
Pansodoro *et al*. [201]	Penile: 16%	< 1 cm: 71%	< 15 Fr: 34%	Single: 50%	None: 36%
	Penobulbar: 11%	> 1 cm: 18%	> 15 Fr: 69%	Multiple: 16%	1: 6%
	Bulbar: 42%	-	-	-	> 1: 0%
Steenkamp *et al*. [196] / Heyns [214]	RR for recurrence penile vs. bulbar: 1.85 (95% CI: 0.94 to 3.67, p = 0.077)	< 2 cm: 60% (@12 months)	NR	NR	None: 50-60% (@48 months)
	-	2-4 cm: 50% (@12m)	-	-	1: 0-40% (@48 months)
	-	> 4 cm: 20% (@12 months)	-	-	2: 0% (@24 months)
Santucci *et al*. [200]	NR	NR	NR	NR	0: 8%
	-	-	-	-	1: 6%
	-	-	-	-	2: 9%
	-	-	-	-	> 2: 0%
Al Taweel *et al*. [204]	Bulbar: 11%	< 1 cm: 27%	NR	NR	0: 12.1%
	Penile: 0%	1-2 cm: 0%	-	-	1: 7.9%
	Penobulbar: 0%	> 2 cm: 0%	-	-	> 1: 0%
Barbagli *et al*. [203]	NA	1-2 cm: 71% (@60 months)	pQ_{max} < 5 ml/s: 31%	NA	0: 62%
	-	2-3 cm: 51% (@60 months)	pQ_{max} 5-8 ml/s: 53%	-	1: 37%
	-	3-4 cm: 39% (@60 months)	pQ_{max} > 8 ml/s: 83%	-	-
Kluth *et al*. [202]	Location no predictor	NR	pQ_{max} no predictor	NR	0: 60%
	-	-	-	-	≥ 1: 39%
Pal *et al*. [205]	NA	< 1 cm: 45%	NR	Single: 35%	0: 30%
	-	1-1.5 cm: 0%	-	Multiple: 0%	1: 23%
	-	> 1.5 cm: 0%	-	-	2: 13%

Launonen [206]	Bulbar: 76%*	< 2 cm: 83%*	NR	NR	0: 26%
	Penile: 71%*	> 2 cm: 0%*	-	-	1: 33%
	-	-	-	-	2: 26%
	-	-	-	-	3: 11%
	-	-	-	-	4: 0%
Redon-Galvez [207]	NR	≤ 1 cm: 71%	NR	NR	NR
	-	> 1 cm: 25%	-	-	-

DVIU = Direct vision internal urethrotomy; NA = not applicable; NR = not reported; pQmax = pre-operative maximum urinary flow.
**patency rates are reported after repetitive treatments.*

6.2.1.2 Indications of "hot-knife" direct vision internal urethrotomy

6.2.1.2.1 Laser urethrotomy

Lasers available for urological applications, including Neodymium:YAG, Argon, Holmium:YAG, Potassium titanyl phosphate (KTP) and Tm:Yag, have been used for the treatment of urethral strictures. A SR identified four RCTs comparing laser urethrotomy and the "cold knife" urethrotomy. All studies were limited by short-term outcome evaluation and none of these four studies specified the results based on the location of the stricture. Two of these studies reported specific recurrence rates and meta-analysis showed a RR for recurrence of 0.55 (95% CI: 0.18-1.66; p=0.29), 0.39 (95% CI: 0.19-0.81; p=0.01) and 0.44 (95% CI: 0.26-0.75; p=0.003) in favour of laser urethrotomy after three, six and twelve months respectively [218]. Jin *et al*., performed a SR including 44 case series on laser urethrotomy or "cold knife" DVIU [213]. This included nineteen articles on laser urethrotomy and 25 articles on "cold knife" DVIU. The overall weighted average stricture-free rate was 74.9% (371/495) and 68.5% (1874/2735) for laser vs. "cold knife" DVIU, respectively (p=0.004). Although statistically significant, the results must be interpreted with caution because of heterogeneity and because no details are provided on follow-up duration. Specifically looking at first DVIU, laser and "cold knife" DVIU obtained a stricture-free rate of 58.6% and 42.7% respectively and the difference was no longer statistically significant (p=0.09). At the bulbar urethra, laser and "cold knife" DVIU yielded a stricture-free rate of 52.9% and 60%, respectively (p=0.66) [213].

After publication of this SR, the EAU Guideline Panel scope search identified two additional RCTs [219, 220] and one retrospective cohort series [221]. In the RCT of Yenice *et al*., patients with a primary, bulbar stricture were randomised either to "cold knife" DVIU (n=29) or holmium:YAG laser urethrotomy (n=34). After twelve months follow-up, no significant difference in patency rate was identified (79% for "cold knife" DVIU vs. 68% for laser urethrotomy, p=0.3) [220]. In their RCT, Chen *et al*., reported a better patency rate after one year with laser (n=24) compared to "cold knife" (n=22) DVIU (respectively 88% vs. 18%; $p < 0.05$). However, after two years the benefit for laser disappeared and after five years both techniques showed a low patency rate: 9% for "cold knife" DVIU vs. 12% for laser DVIU ($p > 0.05$) [219]. In both these RCTs, operation time was slightly but significantly longer with laser DVIU as compared to "cold knife" DVIU [219, 220]. Holzhauer *et al*., evaluated in a retrospective comparative study "cold knife" (n=127) with laser (n=65) DVIU at a mean follow-up of sixteen and eighteen, respectively. They reported patency rates of 42% for "cold knife" DVIU vs. 31% for laser DVIU (p=0.1) [221].

6.2.1.2.2 Plasmakinetic (bipolar) urethrotomy

Cecen *et al*., conducted an RCT comparing plasmakinetic with "cold knife" DVIU (n=136) [222]. They reported patency rates for plasmakinetic and "cold knife" urethrotomy at nine months in respectively 86% and 70% of cases (p=0.025). At eighteen months, patency rates for plasmakinetic and "cold knife" urethrotomy were 63% and 67%, respectively (p=0.643) [222]. A prospective cohort study on primary strictures < 2 cm reported a patency rate at twelve months in 23/30 (77%) cases for plasmakinetic DVIU vs. 19/30 (63%) cases with "cold knife" DVIU (p=0.04) [223]. A retrospective case series (n=27) reported a 74% patency rate for short (1-2.5 cm) strictures after a mean follow-up of fourteen months [224]. They reported negligible blood loss during the procedure and no post-operative incontinence.

Based on the conflicting results described above and considering the heterogeneity of series and absence of long-term follow-up, overall, the available studies do not support the efficacy of one technique of DVIU over another. Given the similar complication rates between techniques (see section 6.2.1.3), no recommendation can be made in favour of one technique over another.

6.2.1.3 Complications of direct vision internal urethrotomy

6.2.1.3.1 Complications of "cold knife" direct vision internal urethrotomy

An overall complication rate of 6.5% was reported in a SR of Jin *et al*., based on twelve articles including 1,940 patients [213] (Table 6.3).

Notably, erectile dysfunction (ED) was reported in 5.3% of cases in this review [213]. In addition, Graversen *et al*., reported ED in eleven out of 104 (10.6%) patients [225]. This risk appears higher in strictures located in the penile urethra and, in addition to the poor patency rates, the use of DVIU in the penile urethra must be discouraged [217, 225].

6.2.1.3.2 Complications of "hot knife" direct vision internal urethrotomy

The SR of Jin *et al*., reported a total complication rate of 11.8% (39/330) [213] (Table 6.3).

6.2.1.3.3 Complications of "cold knife" vs. "hot knife" direct vision internal urethrotomy

In a SR of RCTs comparing "cold knife" DVIU vs. laser DVIU, only 1/4 series reported complications [218]. In the laser group, an 8.9% complication rate was found due to contrast extravasation to the perineum and stricture recurrence. For the "cold knife" DVIU, a 15.5% complication rate was reported related to bleeding [218]. Two later RCT's reported similar rates of urinary extravasation [219, 220] and urinary incontinence (UI) [219] with both techniques.

The SR of retrospective case series of Jin *et al*., found no significant differences in the incidence rates of UI, urinary extravasation and UTI between laser and "cold knife" DVIU [213]. However, urinary retention and haematuria were more frequent with laser compared to "cold knife" DVIU [213]. Conversely, In the series of Yenice et al., haematuria was only reported after "cold knife" DVIU but not after laser DVIU (p=0.6) [220] (Table 6.3).

Table 6.3: Complications after "cold knife" DVIU vs. laser DVIU

Study/Complication	"Cold knife" DVIU (%)	Laser DVIU (%)	p-value
Jin *et al*. [213]			
Urinary extravasation	2.9	3.1	0.938
Urinary incontinence	4.1	2.1	0.259
Urinary tract infection	2.1	2.7	0.653
Urinary retention	0.4	9	< 0.0001
Haematuria	2	5.2	0.034
Epididymitis	0.5	NR	NA
Fever	2.3	NR	NA
Scrotal abscess	0.3	NR	NA
Erectile dysfunction	5.3	NR	NA
Urinary tract irritation	NR	11.4	NA
Urinary fistula	NR	1.5	NA
Dysuria	NR	5.1	NA
Yenice *et al*. [220]			
Urinary extravasation	0	2.9	0.6
Haematuria	10	0	
Chen *et al*. [219]			
Urinary extravasation	9.1	4.2	0.5
Urinary incontinence	4.5	4.2	

DVIU = direct vision internal urethrotomy; NA = not applicable; NR = not reported.

6.2.1.3.4 Complications of direct vision internal urethrotomy vs. dilatation

A Cochrane review found no significant differences for overall intra-operative complications (single dilatation vs. DVIU respectively 14% vs. 11%; RR: 0.75; 95 CI: 0.36-1.55) nor for individual complications (difficulty urinating, haematuria, false passage, pain, knotting/breaking/bending filiform leader) [196, 197]. The low rate of false passage for both DVIU and dilatation (respectively 0.96 and 0.94%) might be explained by the systematic use of a filiform leader in both groups which was inserted endoscopically in the dilatation group followed by coaxial dilatators [196, 197].

A small retrospective study comparing balloon dilatation (n=31) with DVIU (n=25) showed less urethral bleeding (6.5 vs. 32%; p=0.017) and UTI (3.2 vs. 24%; p=0.037) with balloon dilatation [226].

Apart from acute peri-operative complications described above, the stricture length was reported to increase after DVIU treatment requiring complex urethral reconstruction, but the authors of this retrospective study clearly state the limitations of the study design in the absence of consistent baseline investigations [200]. Other

authors mention that repeat urethral manipulations (DVIU and/or dilatation) can increase stricture complexity and delays time to urethroplasty [227, 228].

6.2.1.3.5 Complications of "cold knife" direct vision internal urethrotomy vs. urethroplasty

The OPEN-trial reported adverse events of any type in 61% and 26.1% after urethroplasty (all types) and DVIU respectively [209]. In the urethroplasty group, mouth pain (related to oral mucosa graft [OMG] harvesting) and wound infection was noted as complication in respectively 14.6% and 4.9% of cases. Erectile dysfunction was 4.9% and 2.6% after urethroplasty and DVIU, respectively. Serious adverse events were reported in 8.5% and 8.7% after urethroplasty and DVIU respectively [209].

Summary of evidence	**LE**
Direct vision internal urethrotomy performs poorly in penile strictures. Direct vision internal urethrotomy at the penile urethra might provoke venous leakage from the corpora cavernosa with subsequent risk of erectile dysfunction.	1b
Increased stricture length is associated with higher risk of failure of DVIU.	1b
In selected patients with a primary, single, short (< 2 cm) and non-obliterative bulbar stricture, a five-year stricture-free rate of up to 77% can be expected.	3
Direct vision internal urethrotomy has a stricture-free rate of 51-71% if performed for a short (< 2 cm) recurrent stricture after prior bulbar urethroplasty.	3
There is conflicting evidence that "hot knife" (laser, plasmakinetic) DVIU would be superior compared to "cold knife" DVIU after more than one year of follow-up.	1a

Recommendations	**Strength rating**
Do not use direct vision internal urethrotomy (DVIU) for penile strictures.	Strong
Do not use DVIU/dilatation as solitary treatment for long (> 2 cm) segment strictures.	Strong
Perform DVIU/dilatation for a primary, single, short (< 2 cm) and non-obliterative stricture at the bulbar urethra.	Weak
Perform DVIU/dilatation for a short recurrent stricture after prior bulbar urethroplasty.	Weak
Use either "hot" or "cold knife" techniques to perform DVIU depending on operator experience and resources.	Weak

*6.2.2 **Single dilatation***

6.2.2.1 Modalities of dilatation and results

Dilatation can be done in the office, under local anaesthesia and without complex resources [216, 229]. With dilatation, the urethral mucosa at the stricture site is stretched and the scarring is disrupted. This is opposed to DVIU where the stricture is incised. However, both treatment modalities use the same principle to achieve urethral patency: a breach of the urethral mucosa at the site of the stricture in which re-epithelialisation should occur faster than wound contraction [197].

When dilators are used to dilate bulbar urethral strictures, considerable experience is required to avoid accidental perforation of the urethra at the level of the stricture. In order to reduce the risks (esp. false passage, spongiosal perforation, urethral bleeding) of "classic" blind dilatation with rigid sounds [229], other strategies have been developed and evaluated in which the dilatation is visually controlled:

- endoscopic/fluoroscopic guidewire placement and progressive dilatation with Amplatz renal dilators [229, 230];
- endoscopic/fluoroscopic guidewire placement and balloon dilatation [226, 231];
- endoscopic/fluoroscopic guidewire placement and S-curved coaxial dilators [232].

Although no direct comparative studies of blind vs. visually controlled dilatation are available, several studies have reported a low complication rate with visually controlled modifications of dilatation. The recurrence rate with short follow-up largely varies between 7.7-64.5% (Table 6.4). Chhabra *et al.,* identified focal/short (< 1.5 cm) strictures and strictures at the bulbar urethra as predictors for a favourable outcome [231].

Table 6.4: Results of visually controlled dilatation

Study	Technique	N	FU (mo)	recurrence	Definition of failure	Complications			
						Haematuria	False passage	Procedural failure	UTI
Akkoc *et al*. [229]	Amplatz	26	12-21	2 (7.7%)	Need for additional intervention	3 (11.5%)	0 (0%)	NR	NR
Chhabra *et al*. [231]	Balloon + ISD (permanent)	144	24 (3-52)	21 (15.6%)	Need for additional intervention	NR	0 (0%)	3 (2.1%)	14 (9,7%)
Kallidonis *et al*. [232]	Coaxial S-curved	310	12	90 (33%)	No recurrence @1 yr with maximum one additional procedure	11 (3.5%)	0 (0%)	7 (2.2%)	33 (10.6%)
Nomikos *et al*. [230]	Amplatz + DVIU + ISD (1 yr.)	34	12	8 (23.5%)	Stricture recurrence on urethroscopy/ urethrography	2 (5.8%)	NR	NR	3 (8.8%)
Yu *et al*. [226]	Balloon	31	15 (5-36)	20 (64.5%)	Need for subsequent urethroplasty	2 (6.5%)	0 (0%)	NR	1 (3.2%)

DVIU = direct vision internal urethrotomy; FU = follow-up; ISD = intermittent self-dilatation; mo = months; N = number of patients; NA = not applicable; NR = not reported; UTI = urinary tract infection; yr = year.

6.2.2.2 Effectiveness of dilatation compared with direct vision internal urethrotomy

A SR identified only one prospective RCT comparing dilatation with DVIU and failed to detect any differences [196, 197]. In a small (n=56) retrospective cohort study, the three-year estimated stricture recurrence-free survival was 35.5% and 28% for respectively balloon dilatation and DVIU (p=0.21) [226].

At present, there is lack of evidence to support the claim that dilatation is superior to DVIU (or *vice versa*) and therefore, the indications for single dilatation are the same as for DVIU.

Repetitive dilatation/DVIU with curative intent (see also section 6.2.1.1.3.6 Previous interventions) should be avoided as no long-term freedom of recurrence can be expected [216] and because of the significant risk of increasing stricture length and complexity [227, 228] and prolonging the time to urethroplasty (which has better patency rates) [228].

Summary of evidence	LE
Visually controlled dilatation after endoscopic or fluoroscopic guidewire placement has a low complication rate.	3
Repetitive dilatations/DVIU have no long-term freedom of recurrence and increase stricture complexity.	1b

Recommendations	Strength rating
Use visually controlled dilatation in preference to blind dilatation.	Weak
Do not perform repetitive (> 2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option.	Strong

6.2.3 ***Post-dilatation/direct vision internal urethrotomy strategies***

Several strategies have been developed and evaluated to prevent wound contraction, improve the stricture-free rate and time to stricture recurrence after dilatation or DVIU.

It is noteworthy that these strategies tend to stabilise the stricture rather than to keep the patient stricture-free and the reported outcomes should be understood in this respect.

6.2.3.1 Intermittent self-dilatation

6.2.3.1.1 Results

A SR identified six randomised and quasi-randomised trials comparing ISD with no ISD with a follow-up between eight and 24 months [233]. Stricture recurrence was reduced in men performing ISD (85/197, 43%) vs. those who did not (128/207, 62%) (RR: 0.70; 95% CI: 0.48-1.00; p=0.05). There was significant heterogeneity, and the quality of included studies was very low, which led the authors to conclude there is uncertainty about the estimate [233]. This review found no significant difference in adverse events between ISD and no ISD (RR: 0.60; 95% CI: 0.11-3.26; p=0.56) [233]. One trial containing 48 patients found no significant difference in six vs. twelve months duration of ISD (RR: 0.67; 95% CI: 0.12-3.64) and another trial (n=59) found no significant difference from using a low-friction hydrophylic vs. a polyvinyl chloride catheter (RR: 0.32; 95% CI: 0.07-1.40) [233]. Other studies have been published after this SR of 2014. Chhabra *et al*., reported that patients complying with ISD after dilatation had a lower need for re-intervention than those who did not, 12.3% vs. 20.5% respectively (p=0.2) [231]. After a mean follow-up of 25 months, Greenwell *et al*., found a need for subsequent intervention in 13/31 (42%) men performing ISD vs. 47/95 (49%) who did not (p=0.46). The number of reoperations in patients with need for subsequent intervention was lower in the group performing ISD vs. those who did not (2.6 vs. 3.4). No major complications were reported in both groups [234].

6.2.3.1.2 Complications

The potential benefit of ISD in stabilising the stricture must be balanced against the drawbacks. Commonly reported complications are urethral bleeding (7.1%) [235] and UTI/epididymitis (4.7-18.1%) [236, 237]. A multicentric prospective study (n=85) reported that respectively 35% and 26% of patients had moderate to severe difficulties in catheterisation and respectively 32% and 17% of patients suffered moderate to severe pain while performing ISD. This had a serious impact on QoL which was rated moderate and poor in 32% and 55% of patients, respectively [35]. Younger age was identified as predictor for poor QoL, and QoL was more impaired in proximal stricture location (posterior and bulbar) [35]. In a study of 286 patients (mainly > 60 years old) performing ISD, 20% experienced problems with ISD and 33% had at least one infection annually. After a mean follow-up of 58 months 67% still continued with ISD [238]. Khan *et al*., reported eight “drop-outs” of 30 (26.7%) men randomised to ISD [237]. Of these eight “drop-outs”, two were unable to perform ISD and one stopped because of pain.

As mentioned above, repetitive dilatation (including ISD) increases stricture complexity and delays time to urethroplasty [227, 228].

6.2.3.1.3 Intermittent self-dilatation combined with intra-urethral corticosteroids

To delay wound contraction at the stricture site, intra-urethral corticosteroids (as a catheter lubricant) have been used to improve the results of ISD. In 2014, a SR identified three prospective RCTs comparing ISD and local steroid (triamcinolone) ointment vs. ISD without local steroid ointment [239]. These three studies included a total 67 and 68 patients randomised to local steroid, or not, with a follow-up ranging between twelve and 36 months. There were fifteen (22.4%) recurrences in the steroid group and 25 (36.7%) in the control group (OR: 0.51; 95% CI: 0.24-1.10; p=0.09) [239]. Time to recurrence was longer in the steroid group vs. the control group (weighted mean difference = 0.29; 95% CI: 0.08-1.00; p=0.05). There was no difference in adverse events between groups [239].

Since 2014, two additional RCTs have been published. Ergun *et al*., evaluated patients after DVIU for primary short (< 2 cm), bulbar (82%) or posterior (18%) strictures that were further randomised between ISD (n=30) and ISD + triamcinolone ointment (n=30) for six weeks. Stricture recurrence rate after 24 months was not significantly different between ISD and ISD + triamcinolone (respectively 33.3 and 30%) [240]. On the other hand, Regmi *et al*., found a lower stricture recurrence rate (22% vs. 46%, p=0.04) in patients performing ISD + triamcinolone (n=27) vs. ISD alone (n=28) [241]. In this study, median time to recurrence was 7.4 ± 4.5 months vs. 11.9 ± 3 months in respectively ISD alone and ISD + triamcinolone (p=0.16). Both studies reported no complications related to ointment of triamcinolone [240, 241].

In a small (n=28) cohort with LS-related strictures, an intra-urethral steroid regimen was successful (no need for subsequent escalation of therapy) in 25 (89%) patients after a mean follow-up of 25 months [155]. This regimen consisted of applying clobetasol cream 0.05% as lubricant on a calibration device (10-16 Fr catheter or dilator) twice a day during a minimum of two months. As most of these patients further continued with instillation of steroids on a calibration device, this high “success” rate must be viewed with caution and should be considered as a stabilisation of the stricture rather than a cure. Eventually, twelve (42.8%) patients could reduce the interval of instillation/dilatation and three (10.7%) of them could finally stop the treatment [155].

Summary of evidence	LE
Stricture recurrence was reduced in men performing ISD vs. those who did not.	1a
Intra-urethral corticosteroids in addition to ISD delays the time to recurrence.	1a

Recommendations	Strength rating
Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/direct vision internal urethrotomy if urethroplasty is not a viable option.	Weak
Use intra-urethral corticosteroids in addition to ISD to stabilise the urethral stricture.	Weak

6.2.3.2 Intralesional injections

The rationale of adjuvant intralesional injections is to reduce fibroblast proliferation and excessive urethral scaring [215].

6.2.3.2.1 Steroids

A 2014 SR identified five studies comparing intra-urethral submucosal steroid injection vs. no intra-urethral submucosal steroid injection after DVIU, of which two were RCTs [239]. Meta-analysis of these two RCTs with 57 and 58 patients in, respectively, the steroid and control group showed no statistical difference in recurrence rate (OR: 0.53; 95% CI: 0.25-1.13; p=0.10).. Time to recurrence was significantly longer in the steroid group (weighted mean difference = 4.43; 95% CI: 2.77–6.09, p < 0.00001). There were no significant differences regarding adverse events (infection, bleeding, extravasation) between both groups (weighted mean difference = 1.59; 95% CI: 0.71–3.58, p=0.26).

6.2.3.2.2 Mitomycin C

An RCT (n=40) by Moradi *et al*., reported that MMC hydrogel significantly reduced recurrent stricture formation (10% with MMC vs. 50% without MMC; p=0.001) at one year in patients with anterior strictures < 1.5 cm and no or mild spongiofibrosis on US [242]. The authors reported no significant complications related to MMC injection [242]. Another RCT (n=151) with eighteen months follow-up in predominantly bulbar strictures reported a stricture-free rate of 86% and 63% after DVIU with and without MMC, respectively (p=0.002) [243]. The mean stricture length was less than 2 cm in both groups. No significant complications, such as necrosis of the urothelium, extravasation, or systemic absorption, were recorded in the MMC group [243].

Farrell *et al.,* conducted a retrospective study in 44 patients with recurrent bulbar and BMS with a median stricture length of 2 cm (IQR: 1-2.5 cm) [212]. They reported patency in 75% after a median follow-up of 26 months. No long-term complications attributed to MMC were observed.

In a prospective case-series (n=103), Kumar *et al*., evaluated adjuvant intralesional injections of a cocktail of triamcinolone, MMC and hyaluronidase after DVIU for predominantly (78%) bulbar strictures with a median follow-up of fourteen months. A stricture-free rate of 81% was reported and none of the patients suffered local or systemic side effects related to the injection [244].

Despite the encouraging results reported with MMC, the use of MMC in urethral stricture management is still off-label and not widespread. Severe complications with MMC injection are possible. Redshaw *et al.,* reported in a multi-institutional series that 4/55 (7%) patients experienced serious complications with osteitis pubis, rectourethral fistula and necrosis of the bladder floor when MMC was injected after endoscopic incision to treat BNS [245]. Given this safety concern and in the absence of well-conducted and adequately powered RCTs, MMC adjuvant to DVIU should only be used in the framework of a clinical trial.

See supplementary Table S6.1 for further information.

6.2.3.2.3 Platelet rich plasma

Rezaei *et al.,* conducted an RCT comparing DVIU + platelet rich plasma (PRP) (n=44) vs. DVIU + saline (n=43) in primary, bulbar strictures < 1.5 cm in length [246]. The two-year stricture-free rate was 78% vs. 56% after DVIU with or without PRP, respectively (p=0.034). Complications were frequent but not significantly different between both groups (DVIU + PRP: 70%; DVIU + saline: 79%). All complications (urethral bleeding, haematuria, urethral pain, pelvic pain, urinary leakage and genitoperineal swelling) were classified as grade 1 according to the Clavien-Dindo system. Further validation of this treatment is needed before general clinical implementation.

Summary of evidence	LE
Intralesional injections after DVIU might improve stricture-free rates on the short-term compared to DVIU alone. Experience is limited and the use of these drugs are off-label.	1a

Recommendation	Strength rating
Do not use intralesional injections outside the confines of a clinical trial.	Weak

6.2.3.3 Urethral stents

Urethral stents are designed with the aim to oppose wound contraction after dilatation or DVIU [247, 248]. Stent insertion is a short procedure (< 60 minutes) that can be done under local or spinal anaesthesia as "one-day" surgery [247, 249, 250]. Urethral stents are classified as permanent or temporary (removable, after six to twelve months).

6.2.3.3.1 Results

Permanent stainless-steel mesh stents are no longer commercially available. An RCT comparing dilatation/DVIU only vs. dilatation/DVIU followed by temporary stent insertion for bulbar strictures reported a significantly longer stricture-free survival time in favour of dilation/DVIU followed by stent (median 292 vs. 84 days; $p < 0.001$) [251]. Only 20.6% of patients treated with a stent developed a recurrent stricture within one year vs. 82.8% in the control group. These results are corroborated by a prospective series of Wong *et al*., who found a median stricture-free survival of two months after DVIU alone vs. 23 months after DVIU followed by temporary (three months) stent for bulbar strictures [248].

Failure and need for re-intervention are frequent (30-53%) and are usually because of stricture recurrence, stent encrustation, stent migration and urethral hyperplasia. Other complications include recurrent UTI, recurrent haematuria and genito-perineal pain (Table 6.5). Although stents are mainly used to treat bulbar strictures, they have been used for posterior stenoses as well. Stents used in the posterior urethra have a high risk (82-100%) of causing UI and this is most pronounced in patients with previous irradiation and/or strictures extending into the membranous or bulbar urethra [252]. In the bulbar urethra, the risk of UI is higher if stent placement is adjacent to the external sphincter [253]. The use of stents in the penile urethra is anecdotal. Jung *et al*., reported stent failure in 4/7 (57%) patients with a penile stricture after a mean follow-up of eight months. Of those patients who failed, no patient with distal or pan-penile strictures was rendered stricture-free [254]. In their series, stricture recurrence after stenting of the penile urethra was significantly higher when compared to the bulbar urethra [254]. Although no direct comparison is available, temporary stents tend to have fewer and less severe complications compared to permanent stents (Table 6.7).

Table 6.5: Failure rate and complications associated with urethral stents

Study	Type of stent	Duration	N	FU (months)	Stricture length (cm)	Stricture location	Previous interventions	Failure rate	Defintion failure	Complications						
										UTI	haematuria	stent encrustation/ stone formation	stent migration	urethral hyper-plasia	Local pain	UI
Abdallah *et al*. [247]	Thermo-expandable nitinol	Temporary	23	17 (6)	3.6 (1.2)	Bulbar	DVIU/ urethroplasty: all	12 (52%)	Need for re-intervention	4 (17%)	3 (13%)	3 (13%)	5 (22%)	2 (8%)	6 (26%)	NR
Jordan *et al*. [251]	Thermo-expandable nitinol	Temporary	63	12	2.7 (1.6)	Bulbar	DVIU only: all	28 (44%)	Inability to pass 16 Fr cystoscope	31 (49%)	10 (16%)	3 (4.7%)	8 (13%)	NR	19 (30%)	12 (19%)
Temeltas *et al*. [250]	Polymer-coated	Temporary	28	29 (7-46)	1.9 (0.5-3.5)	Bulbar	DVIU only: all	10 (36%)	Stricture recurrence on urethroscopy/ graphy, Q_{max} < 15 ml/s, UTI	NR	NR	1 (3.6%)	3 (11%)	NR	0 (0%)	NR
Wong *et al*. [248]	Thermo-expandable nitinol	Temporary	22	23 (9-31)	2.4 (1-4.5)	Bulbar	DVIU only: all	7 (32%)	Inability to pass 17 Fr cystoscope, Q_{max} < 10 ml/s or recurrent obstructive symptoms	0 (0%)	NR	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	NR
Atesci *et al*. [249]	Thermo-expandable nitinol	Permanent	20	144 (120 -192)	2.5 (0.5-5.5)	Bulbar	DVIU/ urethroplasty: all	6 (30%)	Need for re-intervention	NR	NR	4 (20%)	2 (10%)	0 (0%)	8 (40%)	1 (5%)
Sertcelik *et al*. [253]	Thermo-expandable nitinol	Permanent	47	101 (84-125)	2 (0.5-5)	Bulbar (45), bulbomem-branous (2)	urethroplasty (19%)/ DVIU (64%)/ railroading (17%)	22 (47%)	Need for re-intervention	NR	NR	12 (26%)	2 (4%)	7 (15%)	20 (43%)	9 (19%)
Erickson *et al*. [252]	Self-expandable super alloy mesh	Permanent	38	28 (30)	3 (1.7)	Posterior (prostate cancer related); VAUS 24; prostatic urethra (irradition) 14	DVIU only: all	20 (53%)	Need for re-intervention	7 (18%)	3 (8%)	6 (16%)	NR	NR	6 (16%)	31 (82%)

DVIU = direct vision internal urethrotomy; FU = follow-up; NR = not reported; UI = urinary incontinence; UTI = urinary tract infection; VUAS = vesico-urethral anastomotic stricture; Q_{max}= maximum flow rate

6.2.3.3.2 Treatment of stent failure

In the case of stent failure, subsequent urethroplasty (usually with stent removal) is possible, but this urethroplasty is very likely to be more complex than it would have been had it been performed initially [255-257]. Due to the fact that the stainless-steel wires are fully embedded into the urethral wall, over time the urethral spongiosum is severely damaged. Horiguchi *et al*., found that a history of urethral stenting was an independent significant predictor of increased stricture complexity (OR: 13.7; 95% CI: 1.7-318.3; p=0.01) and need for more complex urethroplasty (OR: 6.9; 95% CI: 1.1-64.5; p=0.04) [227]. The majority (62%) of patients in this study had a permanent stent and tend to be difficult to remove because they are epithelialised, usually within six months [227]. The type of urethroplasty required depends on the length of the stricture and quality of local tissues [256]. In the majority of cases, it is possible to preserve the urethral plate and to perform a one-stage substitution urethroplasty [255, 256, 258]. The patency rates after different types of urethroplasty vary greatly between 16.7-100% [255-258] and this variation probably reflects variation in complexity of the stricture, rather than that the superiority of one technique of urethroplasty over another (for further information see supplementary Table S6.2). Due to these limitations, the use of stents should be avoided if subsequent urethroplasty is considered [247, 257]. Urethral stents are not a first-line treatment for urethral strictures but can be considered in co-morbid patients who have a recurrent stricture after DVIU/dilatation and are unable to have more complex urethroplasty or who refuse urethroplasty [247, 251, 252].

Summary of evidence	**LE**
Permanent urethral stents have a high complications and failure rate and make subsequent urethroplasty more challenging if they fail.	3
Stents have a higher failure rate in the penile urethra.	3
Temporary stents after DVIU/dilatation at the bulbar urethra prolong time to next recurrence compared to DVIU/dilatation alone.	1b

Recommendations	**Strength rating**
Do not use permanent urethral stents.	Strong
Do not use urethral stents for penile strictures.	Strong
Use a temporary stent for recurrent bulbar strictures after direct vision internal urethrotomy to prolong time to next recurrence only if urethroplasty is not a viable option.	Weak

6.3 Open repairs (urethroplasty): site and aetiology (clinical scenario) treatment options

*6.3.1 **The role of urethroplasty in the management of penile urethral strictures***

Due to the specific aetiology and the associated problems, strictures related to failed hypospadias repair and LS will be discussed separately. However, many series reporting on the outcome of penile strictures have a mixed aetiology also including failed hypospadias repair and/or LS [259, 260]. Due to their specific location, distal penile strictures will be discussed separately.

6.3.1.1 Staged augmentation urethroplasty

Classically called “two-stage” urethroplasty, this approach may become a multi-stage urethroplasty as revision (usually due to graft contracture) after the 1st stage has been reported in 0-20% of cases [260-263]. Therefore, the term “staged” should be used instead [264]. Revision rates before 2nd stage were 0-20%, stressing that a two-stage urethroplasty might become a multi-stage urethroplasty. In general, reconstructive urologists tend to follow this approach in men with more complex urethral stricture disease (multiple interventions in the past, unfavourable clinical findings such as significant spongiofibrosis or scarring that requires excision, poor quality of the urethral plate). An interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully [265-267].

A SR by Mangera *et al*., has shown an average patency rate of 90.5% with the use of all types of grafts for staged penile urethroplasties with an average follow-up of 22.2 months [268]. Patency rates of staged OMG urethroplasty in specific locations vary between 73.3 and 100% [259, 260, 262, 263]. Post-operative urethrocutaneous fistula (UCF) rates were 17.2% and 2.6% in the studies of Ekerhult *et al.* and Joshi *et al.*, respectively, and either not reported or unclear in the remaining studies [259, 260].

6.3.1.2 Single-stage augmentation urethroplasty

Single-stage urethroplasty offers the option for reconstruction of the stricture without the need for multiple operations, the associated peri-procedural risks, and the cosmetic and functional implications that by definition follow the first part of staged urethroplasties [269-271]. There is some evidence to suggest a considerable

number of patients (50% or more in some studies) who were offered 1st stage urethroplasty never returned for the 2nd stage because they were either satisfied with their functional status after the 1st stage (this particularly applied to older men or patients with multiple failed procedures in the past) or they were disappointed with the need for another operation [269, 270].

In the SR of Mangera *et al.*, overall patency rate for all types of single-staged graft urethroplasties is 75.7% with an average follow-up of 32.8 months [268].

The patency rate for different one-stage techniques in specific are:

- dorsal OMG (n=190): 70-100% [263, 272-277];
- ventral OMG (n=47): 55-92.6% [278, 279];
- dorsal + ventral OMG (n=10): 80% [276];
- double (dorsal + ventral) onlay with penile/scrotal skin graft /OMG (n=14/8/4): 88.5% [273];
- dorsal penile skin graft (n=44): 62-78% [273, 274];
- penile skin flap (n=315): 67-100% [273-275, 280, 281].

No high-level evidence exists to state that one technique is superior to another, but it seems that the dorsal graft location is more commonly used compared to the ventral one. Mangera *et al*., reported that the patency rate was better with OMG compared to other grafts (mainly penile skin) [268]. Jiang *et al*., showed that combined (dorsal + ventral) BMG onlay had significantly better stricture-free rates for penoscrotal strictures (patency rate 88.9% vs. 60.9% with single-onlay approach); however, follow-up was significantly shorter in the double-onlay group [282]. Few studies have reported dedicated results on sexual function parameters that do not appear to be significantly impaired post-operatively [262, 283, 284].

A critical factor with respect to single-staged procedures is the careful selection of patients, as men with long and complex strictures might not be good candidates for single-stage reconstruction and attempts to offer single-staged operations in these patients might lead to higher recurrence rates. Sometimes, this selection can only be done based on intra-operative findings. Therefore, any scheduled single-staged procedure might be converted into a staged one [269, 285]. Palminteri *et al*., highlighted the fact that single-stage augmentation urethroplasties in men with LS-related strictures enlarge rather than remove the diseased segment of the urethra; therefore, there is always a risk of recurrence in the future [286]. The role of previous interventions (especially multiple urethrotomies or history of previous urethroplasties) remains unclear as several studies on single-staged operations do not provide information on previous procedures, or excluded patients with operations in the past [275, 284]. Although favourable outcomes in patients with previous history of urethrotomies/urethroplasties were reported by Barbagli and Kulkarni, in the study by Pfalzgraf *et al*., all recurrences post-previous urethroplasty took place in the single-stage group while Ekerhult *et al*., identified prior history of urethral operations as a risk factor for recurrence in the group of single-stage procedures [259, 262, 263, 273]. In addition to previous urethral surgery, high BMI has also been identified as a poor prognostic factor after single-stage penile urethroplasty [259].

6.3.1.3 Anastomotic urethroplasty in men with penile urethral strictures

Historically, the use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively [267, 287]. Nevertheless, it has been performed in selected patients with very short strictures (usually < 1 cm) with a 93% patency rate, with satisfactory QoL and sexual function and without any case of chordee [288].

Summary of evidence	**LE**
Stricture-free rates for single-stage penile augmentation urethroplasties range from 70-100% for dorsal OMG augmentation, 67-100% for penile skin flap (PSF) augmentation, 55-92.6% for ventral OMG augmentation and 62-78% for dorsal SG augmentation. Overall stricture-free rates for staged OMG penile augmentation urethroplasties range from 70-100%.	2b
In staged urethroplasties, an interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully.	4
The use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively. Anastomotic urethroplasty can be offered in selected cases of very short (< 1 cm), injury-associated penile strictures.	3
In case of adverse intra-operative findings, a single-stage approach might not be feasible and must be converted into a staged approach.	3

Recommendations	Strength rating
Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or staged approach taking into consideration previous interventions and stricture characteristics.	Strong
Offer an interval of at least four to six months before proceeding to the second stage of the procedure provided that outcome of the first stage is satisfactory.	Weak
Do not offer anastomotic urethroplasty to patients with penile strictures > 1 cm due to the risk of penile chordee post-operatively.	Strong
Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in the face of adverse intra-operative findings.	Strong

6.3.1.4 Specific considerations for failed hypospadias repair-related strictures

The term "failed hypospadias repair" (FHR) includes a wide range of abnormalities after previous attempts for reconstruction, such as glans deformity, recurrent urethral stricture, glans/urethral dehiscence, UCF and penile chordee [289-291]. The management of FHR is challenging as the urethral plate, penile skin and dartos fascia are often deficient/non-existent. Management of these patients is often made more difficult due to incomplete health records and a lack of critical information (original meatal site, number, and type of previous repairs) [265, 292]. In addition, multiple operations might need to be offered to reach satisfactory outcomes [289]. As a result, FHR should always be considered as a complex condition and it is advised that FHR management takes place in high-volume centres [290, 291, 293, 294].

"Hypospadias cripples" is a term widely used to describe the group of men with multiple previous failed attempts to correct the condition resulting in unfavourable results such as severe scarring, penile deformity and shortening, hair or stones in the urethra, UCF, chordee and functional disorders (e.g., urinary, or sexual dysfunction). This term should be avoided and a more neutral one should replace it as it further stigmatises men with hypospadias who have been shown to have reduced self-esteem and confidence due to unsatisfactory cosmesis, and problematic urinary and sexual function. Moreover, it has been reported that FHR patients experience high rates of disappointment after failure of attempted repair and a sense of helplessness as they are frequently advised that their failed hypospadias is too complex to correct and they should not pursue further repair [290-292, 295, 296].

Two main approaches are applicable: single-stage or staged procedures. In general, it is advised that staged procedures should be followed when the urethral plate is inadequate for a single-stage operation. Surgeons should consent patients for both types of urethroplasty as the surgical approach might need to be modified intra-operatively depending on favourable/unfavourable intra-operative findings. Besides poor-quality of the urethral plate, these unfavourable findings include high degree of scarring and presence of concomitant LS, UCF and/or chordee. It is not uncommon for men with FHR to have scarred skin or concurrent LS and thus, skin grafts or flaps should be avoided as the risk of recurrence due to LS is very high (90% in long-term follow-up as reported by Depsaquale *et al*. [41]) [297, 298].

Staged repairs (using mainly BMG) reported patency rates ranging from 71-95% [261, 295, 297, 299, 300], while single-stage repairs had patency rates from 80-100% [297, 299, 301-304]. It needs to be highlighted that, as FHR is an umbrella term that covers various clinical conditions apart from urethral stricture disease only (such as UCF, chordee, penile deformity), "success" rates as reported by the authors in their studies do not represent urethral patency rates only. Unfortunately, the number of previous operations is either not reported or refers to the whole FHR study group collectively rather than to the subgroups of staged/single-staged procedures.

A comparative analysis is reported by Barbagli *et al*., in 345 FHR patients at five-year follow-up. Overall failure-free survival rate was 48% for all urethroplasties, and in sub-analysis, staged techniques had significantly lower treatment failure-free survival rates compared to single-stage techniques [305]. However, it is unclear whether these groups were comparable in terms of baseline characteristics such as age, length of stricture, number of procedures, comorbidities etc. [305]. If the patients in the staged group had a more unfavourable background, this on its own could explain the final outcome rather than the surgical approach itself.

Kozinn *et al*., reported a 16% and 14% revision rate after the 1st and 2nd stage, respectively, and observed that these revision rates were higher in the FHR group compared to non-FHR patients with penile strictures [261]. There is conflicting evidence whether FHR as aetiology is a poor prognostic factor in the outcome of urethroplasty for penile strictures [259, 306-308]. Concomitant UCF can be successfully managed at the same time of urethroplasty [305].

For further information see supplementary Table S6.3.

Summary of evidence	LE
Men with FHR have history of multiple interventions, and poor-quality tissues, and might require complex procedures for a satisfactory functional and cosmetic outcome.	4
Men with FHR may have low self-esteem due to urinary and sexual dysfunction and unsatisfactory cosmesis.	2b
Men with FHR can have scarred penile skin or concurrent LS and outcomes with skin grafts or flaps can be unsatisfactory.	3

Recommendations	Strength rating
Men with failed hypospadias repair (FHR) should be considered complex patients and referred to specialist centres for further management.	Weak
Propose psychological and/or psychosexual counselling to men with unsatisfactory cosmesis and sexual or urinary dysfunction related to FHR.	Weak
Do not use penile skin grafts or flaps in failed FHR patients with lichen sclerosus or scarred skin.	Strong

6.3.1.5 Specific considerations for lichen sclerosus-related penile urethral strictures

Given the fact that LS affects the skin, the use of genital skin as a flap or graft is not advised as the risk of disease recurrence has been reported to be high (50-100%) and while most of recurrences tend to occur within the first two to three post-operative years, late recurrences have been reported [309].

Main strategies are single-stage or staged oral mucosa graft urethroplasty.

The EAU Urethral Strictures Guidelines Panel conducted a SR [6] to explore the role of single-stage oral mucosa graft urethroplasty in the management of LS-related urethral strictures and to compare its outcomes with alternative management options (surgical dilatations +/- ISD; surgical dilatations + local steroids +/- ISD; staged oral mucosa urethroplasty; penile skin urethroplasty; meatotomy/meatoplasty; urethrotomy [Otis, DVIU]; perineal urethrostomy; urinary diversion [e.g., suprapubic catheterisation]).

In total, fifteen studies met the inclusion criteria, recruiting a total of 649 patients (366 from five non-randomised comparative studies and 283 from ten, single-arm retrospective observational studies). Single-stage OMG urethroplasty resulted in success rates ranging from 65-100% after twelve to 67 months mean or median follow-up. For staged OMG urethroplasty, the most commonly reported comparator, the success rates were somewhat lower and varied between 60-79%. Methodological issues (mainly selection bias) could explain the difference in success rates rather than the intervention itself. Complications were uncommon (0-12%) and mainly comprised Grade 1-3 events.

Due to the overall very poor quality of evidence, the SR did not provide a clear answer as to whether single-stage OMG urethroplasty is superior to other management options, although careful patient selection is highlighted. In the absence of adverse local tissue conditions, a single-stage approach could lead to high success rates with an improvement in voiding symptoms and QoL.

Summary of evidence	LE
Lichen sclerosus is a skin condition that can lead to scarring, and recurrence rates after skin graft/flap augmentation urethroplasties have been reported to be high (50-100%).	4
Single-stage OMG urethroplasty provides patency rates between 65-100% and is not inferior to staged OMG urethroplasty.	3

Recommendations	Strength rating
Do not use genital skin in augmentation penile urethroplasty in men with lichen sclerosus (LS) related strictures.	Strong
Perform single-stage oral mucosa graft urethroplasty in the absence of adverse local conditions in men with LS related strictures.	Weak

6.3.1.6 Distal urethral strictures (meatal stenosis, fossa navicularis strictures)

Open repair of distal urethral strictures can be in the form of Malone meatoplasty, skin flap meatoplasty or graft (skin [SG]/OMG) urethroplasty.

For short distal meatal strictures, the Malone meatoplasty (dorsal + ventral meatotomy) provides a technique with patency rates up to 100%, and 83% patient-reported satisfaction with the cosmetic results [310].

Skin flap meatoplasty showed excellent patency rates ranging from 85-100% based on three studies comprising 53 patients [311-313]. In addition, based on their results, patient satisfaction with post-operative outcomes and cosmesis was high, there were no cases of ED and functional complaints were minimal (mainly spraying of the urine flow). Barbagli *et al.,* in their study from 2008, had lower success (57%) with the use of skin flaps; however, this was in only seven patients [273].

Patency rates with the use of grafts (OMG or SG) ranged from 69-91% in 85 patients overall [273, 302, 312, 314]. Where reported, patients were satisfied with cosmesis, and mild spraying of the urine flow self-resolved. Although tubularised grafts in a single-stage procedures are not routinely recommended (see also section 9. Tissue transfer), one series reported an 89.9% patency rate for this approach ("two-in one approach") in selected patients with mainly distal penile strictures [315].

For further information see supplementary Table S6.4.

Summary of evidence	**LE**
Post-meatoplasty/urethroplasty patency rates in men with meatal stenosis or fossa navicularis/distal urethral strictures range between 57-100% depending on type of surgical intervention with high patient satisfaction and minimal complications.	3

Recommendation	**Strength rating**
Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures.	Weak

6.3.2 ***Urethroplasty for bulbar strictures***

6.3.2.1 "Short" bulbar strictures

The length of a "short" bulbar stricture is poorly defined. In general, "short bulbar strictures" are those amenable to stricture excision and subsequent tension-free anastomotic repair. The limit is usually around 2-3 cm but can be longer depending on the patient's anatomy and stricture location within the bulbar urethra [316].

In fit patients, the choice of urethroplasty is between EPA (transecting or non-transecting) and FGU.

6.3.2.1.1 Excision and primary anastomosis

6.3.2.1.1.1 Excision and primary anastomosis with transection of corpus spongiosum (transecting EPA)

Transecting EPA (tEPA) is based on the full thickness resection of the segment of the bulbar urethra where the stricture and surrounding spongiofibrosis is located. Reconstruction is performed by a tension-free spatulated anastomosis.

6.3.2.1.1.1.1 Patency rates

The International Consultation on Urological Diseases (ICUD) performed an extensive review of the literature and reported a composite patency rate of 93.8% for tEPA [317]. Based on this, they endorsed tEPA as treatment of choice for short bulbar strictures if other techniques have an expected patency rate below 90%. However, ED was not taken into account for this advice and as discussed below, ED is a concern with tEPA.

After publication of the ICUD review, several other series have been published and the reported patency rates (76-97%) are in line with the findings of the ICUD review [318-330].

Usually, no need for further intervention is used to evidence that the urethra is patent. In the few studies using an anatomic definition for failure (an inability to pass a 16 Fr endoscope) tEPA urethroplasty achieves a similar patency rate, ranging between 85.5-97% [143, 323, 329, 331] (Table 6.12). The median time for recurrence after tEPA is between 3.5 and thirteen months [143, 320, 321].

Several authors suggested that tEPA is the technique of choice for short post-traumatic bulbar strictures with complete obliteration of the urethral lumen and full thickness spongiofibrosis [331, 332]. These strictures are a specific entity and usually the result of a straddle injury with complete or nearly complete rupture of the bulbar urethra. These obliterations are predominantly short and can be treated with tEPA yielding a patency rate of 98.5% as reported in the series of Horiguchi *et al*. [333]. They also reported an improvement in erectile function after urethroplasty measured one year post-operatively. Straddle injury (and perineal trauma) are a common aetiology in papers published about tEPA; however, separate data on the outcomes for this specific aetiology is usually lacking.

For further information see supplementary Tables S6.5 and S6.6.

6.3.2.1.1.1.2 Complications

Granieri *et al*., [322] specifically focused on complications after bulbar urethroplasty. Peri-operative complications (haematoma, neuralgia), infectious complications, anatomic complications and voiding complications were not significantly different between EPA, augmented anastomotic repair (AAR) and FGU. Erectile dysfunction after bulbar urethroplasty is usually transient, with improvement after three to six months [334]. Chordee is one of the complications attributed to EPA urethroplasty but is rarely reported. A large case series (n=352), reported an incidence of 0.3% [331]. Another large case series (n=94), reported five cases (5.3%), with a mean stricture length of 2 cm (range 1.5-4) in patients with this complaint [318].

Other complications of tEPA are a cold feeling in the glans (1.6-3.2%) and decreased glandular tumescence (6%) [334, 335]. These latter complications (as well as ED) might be attributed to complete transection of the corpus spongiosum at the level of the stricture, thereby disrupting the antegrade blood flow of the urethra and corpus spongiosum. To spare this, the non-transecting EPA (ntEPA) has been described [336] and later modified [337].

6.3.2.1.1.2 Non-transecting excision and primary anastomosis

6.3.2.1.1.2.1 Patency rates

Except for straddle injuries that are usually associated with complete obliteration of the lumen and full thickness scarring of the corpus spongiosum [317, 331], ntEPA is a good alternative for short bulbar strictures of all other aetiologies. With median follow-ups ranging between 17.6 and 37.1 months, the patency rates reported are 93.2-99%; with the lack of further intervention as success criteria [330, 332, 338]. Even with the anatomic criteria (16 Fr cystoscopy passage) the success rate achieved was 97.9% at twelve months [331] (see supplementary Table S6.7).

Two comparative analyses evaluated tEPA vs. ntEPA. Waterloos *et al*., reported patency rates of 88.4% and 93.2%, respectively, for tEPA and ntEPA (p=0.33) but with significantly longer follow-up for tEPA (118 vs. 32 months, $p < 0.001$). Of patients scheduled for ntEPA, 11.1% were converted to tEPA, highlighting that ntEPA is not always possible. Chapman *et al*., using anatomic success criteria (16 Fr cystoscope passage), reported patency in 93.8% of tEPA vs. 97.9% of ntEPA. Follow-up was also significantly shorter at 74.1 (SD: 45.4) months for tEPA vs. 37.1 (SD: 20.5) months for ntEPA ($p < 0.001$) [331].

6.3.2.1.1.2.2 Complications

When erectile function after urethroplasty was assessed (at six months), ntEPA had significantly lower ED rates (a decrease of > 5 points on the sexual health inventory for men [SHIM] scale) compared to tEPA (4.3 vs. 14.3%, respectively) [331]. Urethral transection performed during tEPA was the only factor associated with sexual dysfunction in a multivariate analysis [331]. Other series reported ED lasting for more than six months in 2-6% of cases after ntEPA [332, 338, 339]. Grade ≥ 2 Clavian-Dindo complications were 3.6-8.1% vs. 4.3-6.8%, respectively, for tEPA and ntEPA, without reaching statistical significance [330, 331].

To date, no trials comparing ntEPA with FGU have been published to report on comparative patency outcomes and complications.

6.3.2.1.2 Free graft urethroplasty

Despite the very high patency rates of EPA, FGU has been performed for short bulbar strictures as well. This is mainly driven by reports of ED after EPA. A meta-analysis of ten papers [340] comparing tEPA with BMG FGU for short strictures, found that tEPA is better than BMG FGU in terms of patency rates (91.5% vs. 70%), whilst BMG FGU has less erectile complications (9% vs. 25%). However, the methodology of this meta-analysis must be disputed as it was performed on cohort studies without risk of bias assessment and without further specification of timing of assessment of ED. On the other hand, two prospective, non-randomised papers

[143, 341] comparing tEPA with BMG FGU, found no significantly different patency rates for EPA compared to BMG FGU (87-90% vs. 84-87%, respectively) and no significant differences in erectile complications for tEPA compared to BMG FGU (6.7% vs. 2.2%, respectively). However, the operation technique used was dependent upon the length of the stricture, with tEPA utilised for shorter strictures (< 2 cm) and BMG for longer (> 2 cm) [341] or when a tension-free anastomosis was not possible [143]. Appropriate choice of procedure for stricture length and other patient and stricture parameters appear to equalise outcomes. Another prospective trial [342] involving both penile and bulbar strictures could not find any influence on erectile function of urethral transection. A prospective study on ejaculatory function following different urethroplasties by Erickson *et al.,* [343] found no overall difference in ejaculatory score pre- and post-operatively, although patients with a poor score preoperatively improved significantly and those with a good score pre-operatively did not decrease post-operatively.

Dogra *et al*., [283] looked prospectively at sexual function in 87 patients after different urethroplasties (EPA, penile/bulbar substitution) and found a 20% reduction in sexual function in all groups, which resolved after six months.

Details on where to place the graft during FGU are discussed below.

Summary of evidence	**LE**
For short post-traumatic strictures tEPA has good patency rates.	3
For short bulbar strictures not related to straddle injury tEPA, ntEPA and FGU have the same patency rates, but ntEPA and FGU have less erectile dysfunction than tEPA.	3

Recommendations	**Strength rating**
Use transecting excision and primary anastomosis (tEPA) for short post-traumatic bulbar strictures with (nearly) complete obliteration of the lumen and full thickness spongiofibrosis.	Strong
Use non-transecting excision and primary anastomosis or free graft urethroplasty instead of tEPA for short bulbar strictures not related to straddle injury.	Weak

6.3.2.2 "Longer" bulbar strictures

6.3.2.2.1 Free graft urethroplasty

For strictures not amenable to EPA, FGU is the technique of choice and buccal mucosa is, at the moment, the most widely used graft. Other grafts (and flaps) are possible and discussed in the tissue transfer chapter. Patency rates of FGU of the bulbar urethra are 88-91% with twelve to 40 months follow-up [268, 344].

During bulbar urethroplasty, the bulbospongiosus muscle is usually separated at the midline which may cause damage to the muscle and perineal nerves. This might subsequently provoke post-void dribbling and ejaculation disorders. In order to reduce this, the muscle and nerve-sparing perineal approach has been introduced [345]. Although it is mostly used in graft urethroplasty, this approach is also possible for EPA as well [346]. Elkady *et al.,* [339] randomised 50 patients between a muscle and nerve-sparing perineal approach vs. a classic perineal approach and found no difference in operative time (100 vs. 105 min), but significantly less dribbling (4% vs. 36%, p=0.01), and significantly less ejaculatory changes (8% vs. 40%, p=0.02) in the nerve and muscle-sparing group. Fredrick *et al*., [346] did the same in 50 patients in a multicentric study with bulbar urethroplasty but could not find a statistical difference regarding post-void dribbling and ejaculatory changes. Due to the limited and conflicting evidence, no recommendation can be made about the routine use of nerve and muscle-sparing modification during bulbar urethroplasty.

See supplementary Table S6.8 for further information.

6.3.2.2.2 Augmented anastomotic repair

Augmented anastomotic repair is also an option for these strictures. It has been mainly performed in cases where the stricture was just too long (+/- 2-4 cm) for tension-free EPA [328]. It can also be performed for longer strictures with a shorter (nearly) obliterative segment [347]. In this case, only the most obliterative segment is excised, the urethral plate is anastomosed, and the urethra is further reconstructed with an onlay graft [347]. Patency rates after AAR vary between 91.1 - 91.9% with twelve to 28 months follow-up [322, 328] (see supplementary Table S6.9).

A non-transecting alternative has also been described to overcome the previously mentioned inconveniences related to spongiosal transection (augmented non-transecting anastomotic bulbar urethroplasty [ANTABU]). With this technique, Bugeja *et al.,* [348] reported a 100% patency rate in sixteen patients after a median follow-up of thirteen months. One patient (6.7%) suffered permanent ED.

Summary of evidence	LE
For strictures not amenable to EPA, FGU provides an 88-91% patency rate.	1b
Augmented anastomotic repair provides good patency rates for bulbar strictures with a nearly obliterative segment.	3

Recommendations	Strength rating
Use free graft urethroplasty for bulbar strictures not amendable to excision and primary anastomosis (EPA).	Strong
Use augmented anastomotic repair for bulbar strictures not amenable to EPA but with a short, nearly obliterative segment within the whole strictured segment.	Weak

6.3.2.2.3 Location of the graft during urethroplasty for bulbar strictures

The best location for graft positioning into the bulbar urethra remains to be determined. There are many techniques described with ventral, lateral, dorsolateral, or dorsal graft as an onlay or an inlay. Onlay means from the outside onto the urethra, inlay means from the inside after opening the urethra.

Regarding the site of graft placement, the Panel has conducted a SR assessing the literature from 1996 onwards, including studies with at least 20 patients and a minimum of twelve months follow-up [7]. This yielded one RCT, four non-randomised comparative series and 36 case series comprising 3,683 patients. The RCT of Vasudeva *et al.,* compared ventral (n=40) with dorsal (n=40) onlay BMG urethroplasty and reported a patency rate of 90 - 92.5% respectively at twelve months follow-up (p=0.51) [344]. The non-randomised comparative studies could not identify any significant differences in patency rates for dorsal onlay vs. ventral onlay, dorsal inlay vs. ventral onlay or dorsal onlay vs. ventral onlay vs. dorsolateral onlay. Case series reported a patency rate of 62.1-98.3% for dorsal onlay, 74.3-94.4% for ventral onlay and 78.4-92% for dorsal inlay. There are no arguments to assume a higher risk of ED with one of the four techniques. Post-void-dribbling was reported in 0-28.1% with dorsal onlay and in 20-21% with ventral onlay. Other complications were also similar in incidence between techniques. Urethrocutaneous fistula and urethral diverticulum were only reported with the ventral onlay technique although this consisted of only two and one cases, respectively.

Double ventral-dorsal onlay, proposed by Palminteri *et al.,* [144] for high-grade strictures, yielded a patency rate of 91% after 22 months follow-up.

Summary of evidence	LE
Location of the graft has no impact on patency rates.	1b

Recommendation	Strength rating
Use dorsal, dorsal-lateral, or ventral approach according to surgical practice, expertise, and intra-operative findings.	Strong

6.3.2.3 Staged urethroplasty for bulbar urethral strictures

6.3.2.3.1 Indications

Staged urethroplasty may be considered when:

- there are locally adverse conditions such as fistula, false passage, abscess, cancer [285, 349, 350];
- there has been a previously unsuccessful complex urethroplasty including failed hypospadias repair [261, 349];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient [349];
- the stricture is radiotherapy induced [261];
- the stricture is consequent to LS [261] (this is controversial and for some groups LS is a contraindication for a staged urethroplasty [307]; Kozinn *et al*., recommend leaving at least ten months between 1st stage and 2nd stage re-tubularisation in patients with LS to allow graft complication to develop) [261];
- there is severe spongiofibrosis [351].

6.3.2.3.2 Outcomes

Patency rates of 33.3-94.6% at mean follow-up of 11.2-50 months have been described for staged urethroplasty in series which include men with bulbar urethral stricture disease [261, 307, 329, 351-353]. Grafts (mesh graft, preputial skin, oral mucosa) can be used in staged augmentation as well as marsupialisation [329, 351]. In patients affected by LS, a 52.2% patency rate for staged urethroplasty was reported whereas this was 86% for single-stage buccal mucosa urethroplasty ($p < 0.01$) [307]. It is highly likely that different stricture and patient characteristics contributed to the differences reported and this should be kept in mind when interpreting the data. Of note, 19-45.5% of patients planned for staged urethroplasty declined to proceed to 2nd stage re-tubularisation [261, 352].

Early complications after staged procedures include wound dehiscence, UTI, epididymitis, scrotal abscess, and penile numbness. Specific to 2nd stage Johanson urethroplasty UCF occurs in 3-15%. The actual incidence of UCF is probably higher as many small fistulae close spontaneously with conservative management and are not formally reported [307, 329, 351].

Late complications of 1st stage urethroplasty include a need for revision in up to 19% - as a consequence of recurrence of LS in graft(s) (8.8%), graft contracture (6.6%) and stomal stenosis (3.3%) [261]. Late complications of 2nd stage urethroplasty include post-micturition dribble in 14-18%, SUI in up to 16%, penile curvature in up to 9%, ED in up to 4%, urethral diverticulum formation in 1% and cold glans [307, 351, 353]. Stress urinary incontinence, penile curvature and ED appear to be particularly associated with mesh graft stage urethroplasty [351, 353].

After their procedure, 86% and 96.6% of men with, respectively, mesh graft and buccal mucosa graft staged urethroplasty were satisfied. The patient groups included in the review were too small to detect significant differences [351]. All are retrospective series – with heterogenous indications, stricture locations (not exclusively bulbar), stricture lengths and patient groups. It is consequently difficult to draw meaningful conclusions from the little data that are available.

See supplementary Table S6.10 for more information.

Summary of evidence	LE
Staged urethroplasty for bulbar strictures and for strictures involving the bulbar urethra yields patency rates of 33.3-90% depending upon patient and stricture characteristics and patient satisfaction is high with all types of staged urethroplasty.	3
Lichen sclerosus is a relative contraindication for staged urethroplasty in the literature with lower long-term urethral patency rates of 52.2% compared to urethral patency rates of 64.3% in non-lichen sclerosis patients.	3
Up to 45.5% of men elect not to proceed to 2nd stage re-tubularisation after successful 1st stage.	3
Up to 19% of men required revision of their 1st stage urethroplasty.	3

Recommendations	Strength rating
Offer staged urethroplasty to men with complex anterior urethral stricture disease not suitable for single stage urethroplasty and who are fit for reconstruction.	Weak
Do not perform staged bulbar urethroplasty for lichen sclerosis if single stage urethroplasty is possible.	Weak
Consider staged procedure in patients unsure about perineal urethrostomy vs. urethral reconstruction.	Weak
Warn men that staged urethroplasty may comprise more than two stages.	Weak

6.3.2.4 Risk factors for adverse outcomes

In four series specifically dedicated to risk factors for failure after urethroplasty using multivariate analysis, there is conflicting evidence about several factors (aetiology, comorbidity, stricture length, prior therapy) that might be predictive for failure after urethroplasty (Table 6.6). Advanced age does not appear to be a risk factor for urethroplasty failure in the majority of studies, with the exception of Viers *et al.,* 2017 [354] retrospective case series which found that the risk for recurrence was significantly higher beyond the age of 60 (< 50 yrs 94%, > 70 yrs 74%) in 184 patients having a wide variety of urethroplasties. Previous radiation therapy was also found to be a risk factor for stricture recurrence in both Viers' [354] retrospective case series and Ahyai's 2015 series [355] – with only a 71% patency rate at a median follow-up of 29 months in those with previous radiotherapy. Based on these data, a clear and evidence-based recommendation cannot be formulated.

Table 6.6: Risk factors for failure after urethroplasty based on multivariable Cox regression analyses

Study	N	Population	Comorbidity HR (95% CI)	Length HR (95% CI)	Aetiology HR (95% CI)	Prior stricture therapy HR (95% CI)
Breyer *et al*. 2010 [356]	443	Mixed	NS	NS	NS	Prior DVIU: 1.7 (1.0-3.0) Prior urethroplasty: 1.8 (1.1-3.1)
Kinnaird *et al*. 2014 [357]	604	Mixed	NS	≥ 5 cm: 2.3 (1.2-4.5)	Iatrogenic: 3.4 (1.2-10.0) LS: 5.9 (2.1-16.5) Infectious: 7.3 (2.3-23.7)	NS
Chapman *et al*. 2017 [323]	596	Isolated bulbar strictures	Overall comorbidity: 2.4 (1.1-5.3) Obesity: 2.9 (1.3-6.5)	1.2 (1.1-1.3)	Infectious: 3.7 (1.3-10.6)	NS
Verla *et al*. 2020 [358]	474	Anterior strictures	NS	NS	NS	NS

CI = confidence interval; HR = hazard ratio; LS = lichen sclerosus; N = number of patients; NR = not reported NS = not significant.

6.3.2.5 Management of recurrence after bulbar urethroplasty

Kahokehr *et al*., [328] followed nearly 400 patients after urethroplasty and found a recurrence rate of 6% (n=25). Ninety-two percent of the failed cases were treated successfully with DVIU and only 8% needed another open reconstruction. However, they did not mention characteristics of the recurrent cases nor the duration of follow-up.

Rosenbaum *et al.,* [359] and Javali *et al.,* [360] retrospectively analysed the outcomes of BMG FGU for ReDo urethroplasty in 51 and 21 patients, respectively, using the other cheek as donor side. Patency rates were 82-86%, which is in the range of primary cases.

Vetterlein *et al.,* [361] compared primary (no previous open urethroplasty) vs. ReDo (previous open urethroplasty with BMG) vs. secondary (previous open urethroplasty without use of BMG) cases in a retrospective series of 534 patients with BMG FGU. The patency rates in primary and ReDo cases were comparable (87%) whilst the outcome in secondary cases was worse (71%).

A small series (n=37) reported on the use of EPA for revision surgery after failed urethroplasty in strictures of 2.1 (range 1-3.5) cm length on average. Patency rates using EPA after failed primary EPA (51%) and after any other technique of urethroplasty (49%) were 95 and 94% respectively with a mean follow-up of 30 months [321].

Summary of evidence	LE
Buccal mucosa free graft urethroplasty after failed urethroplasty achieves the same patency rates as primary cases.	3

Recommendation	Strength rating
Use oral mucosa free graft urethroplasty for ReDo urethroplasty in case the of a long stricture.	Strong

6.3.3 ***Urethroplasty for penobulbar or panurethral strictures***

The possibilities for reconstruction are various and often include combinations of different techniques or grafts other than OMG. The patency rates are usually lower than in shorter reconstructions (Table 6.7). Hussein *et al.,* [362] performed a RCT comparing skin grafts vs. skin flaps in strictures of mean length 15 cm and found no difference in patency rates (72% vs. 79%) or complications.

Warner *et al*., [307] performed a multi-institutional review in 2015 including 466 patients with stricture length > 8 cm and found an overall patency rate of 77.5%.

As discussed previously, Kozinn *et al.,* [261] reported on the outcome of staged urethroplasty in a cohort of which 54.9% had panurethral strictures (Table 6.7).

Kulkarni *et al*., [363] proposed a one-stage completely perineal approach with invagination of the penis and one-sided urethral dissection. After 59 months the overall patency rate was 83.7% in 117 men with a mean stricture length of 14 cm.

Another option in patients refusing or unfit for complex reconstructive surgery is PU (see section 6.3.4 Perineal urethrostomy).

Table 6.7: Study characteristics and patency rates of series on penobulbar strictures

Author	Study	Length in cm (min, mean, range)	Technique	N	FU months (mean, range)	Patency
Hussein *et al*. 2011 [362]	RCT	NR, 15, 9-21	Skin graft vs. flap	37	36, 12-60	72 vs. 79%
Hussein *et al*. 2016 [364]	Prospective	NR, 8, NR	BM vs. skin dorsal onlay	69	56, NR	90 vs. 84%
Warner *et al*. 2015 [307]	Retrospective review	> 8, 12.5, 8-24	BM/staged/skin	466	20, 12-344	77.5%
El Dahshoury *et al*. 2009 [365]	Retrospective	NR, 18, 15-20	Skin flap	30	24, NR	87%
Mathur *et al*. 2010 [366]	Retrospective	NR, 12, 8-16.5	Tunica albuginea graft	86	36, NR	89%
Meeks *et al*. 2010 [367]	Retrospective	NR, 11, 4-24	Abdominal skin graft	21	28, 11-52	81%
Kulkarni *et al*. 2012 [363]	Retrospective	NR, 14	BM dorsal onlay	117	59, NR	83.7%
Tabassi *et al*. 2014 [368]	Retrospective	NR, 14.4, NR	BM dorsal onlay	117(37)	19, NR	84%
Xu *et al*. 2017 [303]	Retrospective	> 8, 12, 8-20	BM/LM/combination	81	>12, 41, 15-86	83%
Alsagheer *et al*. 2018 [369]	Retrospective	> 8, 11.3	BM onlay vs. skin flap	50	NR, 16, NR	70 vs. 77%
Kozinn *et al*. 2013 [261]	Retrospective	NR, 9.6, 4-17	Staged urethroplasty	91	15, 12-69	90.1%

BM = buccal mucosa; LM = lingual mucosa; FU = follow-up; N = number of patients; NR = not reported; RCT = randomised controlled trial.

Summary of evidence	LE
Publications about panurethral urethroplasties generally come from high volume centres.	4
Different materials and techniques might be needed for reconstruction.	3

Recommendations	Strength rating
Offer panurethral urethroplasties in specialised centres because different techniques and materials might be needed.	Weak
Combine techniques to treat panurethral strictures if one technique is not able to treat the whole extent of the stricture.	Weak

*6.3.4 **Perineal urethrostomy***

6.3.4.1 Indications

Perineal urethrostomy offers a permanent or temporary solution for restoration of voiding in men with complex urethral stricture disease in whom:

- there are no further options to restore urethral patency either due to multiple previous failed urethroplasties [307, 349] or multiple co-morbidities precluding a more expansive surgical undertaking after failed endoscopic management [370];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient;
- following urethrectomy and/or penectomy for cancer [371].

6.3.4.2 Types of perineal urethrostomy

Johanson described an inverted anterior scrotal funnel PU in 1953. This was later modified by Gil-Vernet and Blandy to utilise a posteriorly based scrotal flap. Both these techniques utilise an inverted U or lambda incision. The Gil-Vernet-Blandy PU has been further modified with the addition of dorsal and/or ventral free OMG augment to allow use of PU in men with strictures consequent to radiotherapy [372] or LS [263] and/or in men with PU stenosis or stricture extending into the proximal bulbar or membranous urethra ("augmented Blandy") [370].

More recently, the '7 flap' PU utilising a unilateral posteriorly based scrotal flap has been developed for use in the very obese, or in men of all BMI with stricture extension into the proximal bulbar or membranous urethra [373]. Initially this was performed with transection of the distal bulbar urethra but latterly the technique has been modified to a non-transection technique with loop mobilisation of the bulbar urethra ("loop PU") [374]. The "7-flap" utilises a midline incision – which has been shown to have a significantly reduced side-effect profile in terms of superficial wound infection (1.9% c.f. 18.6%) and superficial wound dehiscence (11.9% c.f. 23.3%) than the inverted U or lambda incision [375, 376] and may be associated with improved urethroplasty (and by inference PU) outcomes, at least in the short term (0% failure c.f. 6.2% failure at six months) [375]. Operative time is similar for all types of PU with mean operative time varying between 97.2 minutes to 112 minutes [371, 377].

The utilisation of PU is increasing [378] – constituting 4.5% of 403 procedures for complex urethral stricture disease in a tertiary centre in 2008 and 38.7% in 2017 [379]. Perineal urethrostomy patients are generally older than those having urethroplasty with a median of 62.6 years of age for men having PU in Fuchs *et al*., 2018 series compared with a median of 53.2 years for men having anterior urethroplasty [379]. Between 18.7% and 73.4% of men having staged urethroplasty for complex anterior urethral stricture decline to proceed to 2nd stage re-tubularisation after a successful 1st stage and remain voiding from the PU of their 1st stage urethroplasty [261, 349, 352].

6.3.4.3 Outcomes

6.3.4.3.1 Patency rates

Patency rates of 70-95% at mean/median follow-up of 20–63 months have been described [307, 349, 354, 370-372, 374, 377, 379]. All reports are retrospective series – all of which are heterogenous in terms of indications and patients. There is consequently little data available to determine which is the best technique for PU.

McKibben *et al*., reported a patency rate of 92.9% in 42 patients for "7-flap" PU at median follow-up of 53.6 months, whilst they had a 100% patency rate with loop PU in twenty patients at a median follow-up of thirteen months [374].

Lumen *et al*., in 2015 reported a 74.3% patency rate for Johanson PU compared with an 87.5% patency rate for Gil-Vernet-Blandy PU (p=0.248), but with a significantly longer follow-up after Johanson PU (median 36 vs. nine months) [371]. Barbagli *et al.,* published the largest series of PU patients to date – including 173 men (all of whom had been planned to have a staged urethroplasty for their complex anterior urethral stricture disease and 127 (73.4%) of whom declined to proceed with 2nd stage re-tubularisation). The median follow-up in this series was 62 months and the patency rate was 70% - confirming that patency rates for PU (and indeed for all urethroplasty [274, 326]) reduce with time [349].

See supplementary Table S6.11 for further information.

6.3.4.3.2 Complications

Perineal urethrostomy complications occur in 2.5-11.4% and include superficial wound dehiscence, scrotal abscess, UTI and urosepsis, bleeding, and transient scrotal pain and numbness [307, 371, 380]. The majority of

complications are Clavien-Dindo grades 1 (2.9-18.8%) and 2 (0-2.9%). Grade 3 complications are rare and only occur in 5.7-6.2%. In the medium-term 22.2-30.8% of men with PU report post-micturition dribble [371].

6.3.4.3.3 Patient reported outcomes

Barbagli *et al*., reported that 168/173 (97.1%) of men were satisfied or very satisfied with the outcome of their Gil-Vernet-Blandy PU and would have the procedure again at median 62 months follow-up. Of these, 166/173 (95.9%) felt they had excellent or good results from their Gil-Vernet-Blandy PU, 145/173 (85%) felt it caused them no problems and 141/173 (82%) felt it caused their partner no problems [349]. The Trauma and Urologic Reconstructive Network of Surgeons (TURNS) collaborative found no significant change in sexual function and a significant improvement in urinary symptoms following PU in a small group of patients [381], whilst Lumen *et al*., found satisfactory or acceptable International Prostate Symptom Score (IPSS) outcomes in 26/32 (81.25%) of men with Johanson or Gil-Vernet-Blandy PU at a median follow-up of 32 months and nine months, respectively.

McKibben *et al*., found a mean patient global impression of improvement (PGI-I) of 1.3 in nineteen patients with either loop PU or "7-flap" PU [374] at median 31 months follow-up.

6.3.4.3.4 Risk factors for patency failure of the perineal urethrostomy

Lichen sclerosus, trauma and infection urethral strictures have poorer outcomes from PU, with PU patency failure in 36.7-67% at a median 62 month follow-up [349, 380]. Worse outcomes were also observed in patients with previous failed urethroplasty and multiple previous endoscopic and open treatments [349, 371, 372].

Barbagli *et al*., found that stricture length was inversely related to PU patency, as was patient age [349]. Conversely Viers *et al*., found outcomes worsened with age, reporting patency rates of 100% in men < 50 years old compared with 83% in men aged 60-69 years old [354]. Lopez *et al*., found increased risk of PU failure in men with ischaemic heart disease which makes sense and would be a putative explanation for the age-related worsening of outcomes noted by Viers *et al*. [380].

Failure of PU is most commonly treated with surgical revision of PU using V-Y plasty, augmentation or complete ReDo but can also be managed with periodic dilatation or urinary diversion [349, 370, 371].

For further information see supplementary Table S6.11.

Summary of evidence	LE
Perineal urethrostomy provides very good short- and long-term outcomes for men with complex urethral stricture disease.	1a
Perineal urethrostomy provides very good short and long-term outcomes for men who are unable to have complex reconstruction due to co-morbidities.	2b
All types of PU yield equivalent very good outcomes.	4
Augmented Gil-Vernet-Blandy or "7-flap" PU yield very good outcomes in men with extension of their urethral stricture disease into the proximal bulbar or membranous urethra.	2
"7-flap" PU yields very good results in obese men.	3

Recommendations	Strength rating
Offer perineal urethrostomy (PU) as a management option to men with complex anterior urethral stricture disease.	Strong
Offer PU to men with anterior urethral stricture disease who are not fit or not willing to undergo formal reconstruction.	Weak
Choose type of PU based on personal experience and patient characteristics.	Weak
Consider augmented Gil-Vernet-Blandy perineal urethrostomy or "7-flap" PU in men with proximal bulbar or membranous urethral stricture disease.	Weak
Consider "7-flap" urethroplasty in obese men.	Weak

*6.3.5 **Posterior urethra***

6.3.5.1 Non-traumatic posterior urethral stenosis

6.3.5.1.1 Treatment of non-traumatic posterior urethral stenosis

Several treatment modalities including conservative management (see section 6.1 Conservative options), endoluminal, open or minimally invasive surgical procedures are currently available, depending on patient's goals and health status.

6.3.5.1.2 Endoluminal management of non-traumatic posterior urethral stenosis

6.3.5.1.2.1 Dilatation of non-traumatic posterior urethral stenosis

This can be done under loco-regional anaesthesia [382-386]. Dilatation is used for VUAS [382-387] or radiation-induced BMS [117, 388] and in the majority of reported cases, patients were not previously treated for their stricture (see supplementary Table S6.12). Patency rates vary widely between 0-89% [117, 382-388]. The risk of *de novo* UI was low (0-11%) and no other complications were reported. It is of note that most series report on visually controlled dilatation [382-386] in VUAS without complete obliteration.

6.3.5.1.2.2 Endoscopic incision/resection of non-traumatic posterior urethral stenosis (Table 6.8)

Incisions can be performed at multiple locations according to surgeon's preference [389]. However, aggressive incisions at the six and twelve o'clock positions should be avoided because of the risk of, respectively, rectal injury and urosymphyseal fistulation [187, 390-392]. The risk of urosymphyseal fistulation is especially a concern after previous radiotherapy [393]. Direct vision internal urethrotomy is mainly performed in patients with primary or recalcitrant VUAS although one series performed it in a mix of patients with VUAS and BNS [394] and two series reported it for radiation-induced BMS [117, 388]. Direct vision internal urethrotomy/dilatation for non-irradiated BMS are usually included in series reporting on anterior strictures (see section 6.2 Male endoluminal treatment of anterior urethral strictures). Patency after a 1st "cold/hot knife" DVIU ranges between 25-80% [382, 385, 387, 389, 394-399]. Laser incision yields a 69-100% patency rate [385, 387, 400, 401]. In a retrospective and unbalanced series, LaBossiere *et al.,* found better patency rates for laser incision as compared to dilatation, "cold knife" DVIU and transurethral resection (TUR) [385]. Redshaw *et al.,* reported inferior patency rates for "cold knife" incision vs. "hot knife" incision followed by MMC for BNS (50 vs. 63%; p=0.03) [240] (see supplementary Table S6.13). Urinary incontinence largely varies between 0 and 53% but some series have not assessed urinary continence before DVIU [395, 397]. In series where pre-DVIU continence data were available, *de novo* urinary continence after DVIU ranges between 0% and 10% [382, 387, 396, 398, 400]. Noteworthy, of 21 patients that were incontinent pre-DVIU in the series of Giannarini *et al.*, eleven (52%) patients became continent, and eight (38%) patients experienced improvement after DVIU [396]. In the series of Lagerveld, 1/5 (20%) patients noticed improvement of UI after DVIU [400]. As most recurrences will occur early [396, 397], it is advised to wait for three to four months after DVIU [389, 397, 402] to proceed with incontinence surgery, if necessary, although others wait for twelve months [403]. The presence of recurrence must be ruled out by cystoscopy prior to incontinence surgery [389, 397, 402, 403].

Another option is to resect the stenosis. Popken *et al*., reported a 47% patency rate with TUR for untreated VUAS and no patient suffered *de novo* SUI [398]. Kranz *et al.,* compared the results of TUR in 87 and 60 patients with, respectively, VUAS after RP and BNS after TURP. After a median follow-up of 27 (range: 1-98) months, patency rate was 40.2% for VUAS and 58.3% for BNS (p=0.031). The rate of *de novo* incontinence was significantly higher in patients treated for VUAS compared to BNS (13.8 vs. 1.7%; p=0.011) [404]. Kravchick *et al*., reported a higher incontinence rate after TUR compared to "cold knife" DVIU and dilatation for VUAS (50% vs. 13% vs. 0%, respectively; p=0.005) [386]. However, the number of patients were small and a selection bias of more severe cases towards TUR might be possible [386]. Alternatively, thermal damage to the adjacent external sphincter during TUR (especially with monopolar current) might be the cause of incontinence [386]. Brodak *et al.,* compared TUR by bipolar resection (n=22) with holmium laser incision and vaporisation (n=17). After a mean follow-up of 42 months, two (9.1%) and four (23.5%) patients suffered a recurrence with bipolar and laser resection respectively (p=0.37). After six months, patients treated with bipolar resection had a significant better Q_{max} compared to laser treatment (13 vs. 6.1 ml/s; $p < 0.001$) [401]. Bipolar plasma vaporisation produced an 82% patency rate at a mean 24-month follow-up in 28 patients with VUAS who previously failed endoscopic treatment [405].

Cut-to-the-light technique for a complete obliterative stricture is not advised because of the very-low likelihood of durable patency and for the risk of false passage towards the rectum [402, 406, 407].

Repetitive DVIU was often able to stabilise the stricture [117, 382, 385, 388, 394-396, 404], but ultimately 6-10% required urinary diversion [397] or chronic suprapubic cystostomy [388, 394].

Transurethral resection can be performed for prostatic obstruction due to sloughing after high-energy treatments (HIFU, cryoablation) [101]. Transurethral resection for obstructive necrotic debris after radiotherapy is possible but is of limited role. Risk of recurrence is 50% and risk of *de novo* UI is 15-25% [101].

Table 6.8: Results of endoluminal incision/resection for posterior non-traumatic stenosis

Study	Modality	Type	N	Previous treatment (%)	FU (months)	Patency° (%)	Urinary incontinence (%)	Complications (%)
Merrick *et al*. [388]	Dilatation/ "Cold knife" DVIU	Radiation-induced BMS	29	0	NR	69	NR	NR
Sullivan *et al*. [117]	Dilatation (n=15) / "Cold knife" DVIU (n=20)	Radiation-induced BMS	39	0	16 (2-48)	51	11	NR
Brede *et al*. [397]	"Cold knife" DVIU	VUAS	63	Dilation 33 Incision 38 Both 29	11 (1-144)	73	52*	NR
Yurkanin *et al*. [395]	"Cold knife" DVIU	VUAS	61	Dilatation 100	31 (1-77)	87	12**	NR
Giannarini *et al*. [396]	"Cold knife" DVIU	VUAS	43	0	48 (23-80)	74	0	NR
Ramchandani *et al*. [382]	"Cold knife" DVIU	VUAS	10	0	NR	80	10	0
Hayashi *et al*. [387]	"Cold knife" DVIU	VUAS	6	Dilatation: 100	NR	50	NR	NR
	Holmium laser DVIU	VUAS	3	Dilatation + DVIU: 100	11-37	100	0	NR
Lagerveld *et al*. [400]	Holmium laser DVIU	VUAS	10	None: 40 Endoscopic (dilatation +/- DVIU +/- ISD): 60	18 (3-29)	100	0	0
Ramirez *et al*. [394]	"Hot knife" DVIU	VUAS: 74% BNS: 26%	50	None: 22	16	72	9	NR
Gousse *et al*. [399]	"Hot knife" DVIU	VUAS	15	None	15 (6-26)	80	100***	NR
Bang *et al*. [389]	"Hot knife" DVIU	VUAS	37	NR	13 (2-33)	65	100***	NR
Popken *et al*. [398]	"Cold knife" DVIU	VUAS	6	None	12-72	50	0	NR
	TUR	VUAS	15	None		47	0	NR
Kranz *et al*. [404]	TUR	VUAS	87	NR	27 (1-98)	40.2	13.8	NR
	TUR	VUAS	60	NR		58.3	1.7	NR
Brodak *et al*. [401]	TUR (bipolar)	BNS	22	DVIU 45	42 (14-72)	91	NR	NR
	Holmium laser DVIU	VUAS	17	DVIU: 12		76	NR	NR
Ozturk *et al*. [402]	TUR (bipolar)	VUAS	28	Dilatation: 75 DVIU: 25	24 (6-66)	82	0	0
LaBossiere *et al*. [385]	Holmium laser DVIU	VUAS	70	NR	10	69	NR	NR
	"Cold knife" DVIU	VUAS	8	NR		25	NR	NR
	TUR	VUAS	36	NR		39	NR	NR

BNS = bladder neck stenosis; DVIU = direct vision internal urethrotomy; FU = follow-up;
ISD = intermittent self-dilatation; NR = not reported; TUR = transurethral resection;
VUAS = vesico-urethral anastomosis stricture.
°patency rate after 1st endoluminal treatment evaluated in the study.
** requiring incontinence surgery (artificial urinary sphincter or male sling).*
*** slightly problematic urinary incontinence by questionnaire post DVIU (no data on pre DVIU continence).*
****all incontinent pre-operatively.*

6.3.5.1.2.3 Post-dilatation/direct vision internal urethrotomy strategies for non-traumatic posterior urethral stenosis

6.3.5.1.2.3.1 Intermittent self-dilatation for non-traumatic posterior urethral stenosis

As for anterior strictures, ISD can be offered to patients for recurrent posterior stenosis after dilation/DVIU to stabilise the stenosis. This is especially relevant for patients unfit/unwilling to undergo surgery or in patients with radiation-induced BMS [117, 385, 388, 408]. Although ISD may be acceptable to many urologists and patients, it usually is associated with a reduced QoL and poor patient compliance [35].

6.3.5.1.2.3.2 Intralesional injections for non-traumatic posterior urethral stenosis

In order to stabilise the luminal fibrosis and consequently to reduce the risk of recurrence, injection of antifibrotic agents at the time of endoluminal treatment has been proposed. The majority of patients in these studies were patients with recalcitrant/recurrent non-obliterative VUAS/BNS. Two series used corticosteroids [386, 402], whilst the others used MMC [245, 403, 406-409]. Patency rates with corticosteroid injections range between 50-100% [386, 402]. Patency rates with MMC vary between 50-79% [245, 403, 406-409]. No trials comparing endoluminal treatment with or without adjuvant intralesional injections were identified.

See supplementary Table S6.13 for further information.

Complications are low across most studies, but all studies were retrospective in nature. Redshaw *et al*., also reported grade 3 complications in four out of 55 (7%) patients, including osteitis pubis (n=2), bladder neck necrosis (n=1) and rectourethral fistula (n=1) in one multi-institutional study [245]. Three of these patients ultimately required urinary diversion with additional faecal diversion in one patient [245]. Given the severity of these complications, although rare, MMC should not be used outside the framework of a clinical trial [410].

6.3.5.1.2.3.3 Urethral stent for non-traumatic posterior urethral stenosis

Stents have been used anecdotally in the posterior urethra [252, 253, 385]. Patency rates are relatively low (47-60%) [252, 253, 385] at the cost of a high-risk for UI (19-82%) [252, 253].

Summary of evidence	**LE**
For non-obliterative VUAS and radiation-induced BMS, visually controlled dilatation and DVIU yield a patency rate of respectively 0-89% and 25-100% with a low complication rate. It can be performed under loco-regional anaesthesia.	3
During DVIU, deep incision might provoke injury to the rectum at the six o' clock position and might provoke uro-symphyseal fistulation at the twelve o'clock position.	3
For BNS, TUR and "hot-knife" incision yield a patency rate of respectively 58.3 and 72% with a low complication rate.	3
Repetitive endoluminal treatments in non-obliterative VUAS, radiation-induced BMS or BNS can stabilise the posterior stenosis and are easy to perform compared to reconstructive surgery.	3
Any form of endoluminal treatment might be associated with *de novo* UI (up to 25%) or worsening of existing UI (up to 15%).	3
Vesico-urethral anastomosis stricture, BMS and BNS with complete obliteration are not included in present series and endoluminal treatment is unlikely to be successful.	3
Urethral stents at the posterior urethra have a rather low patency rate (47-60%) and incontinence rate (19-82%).	3

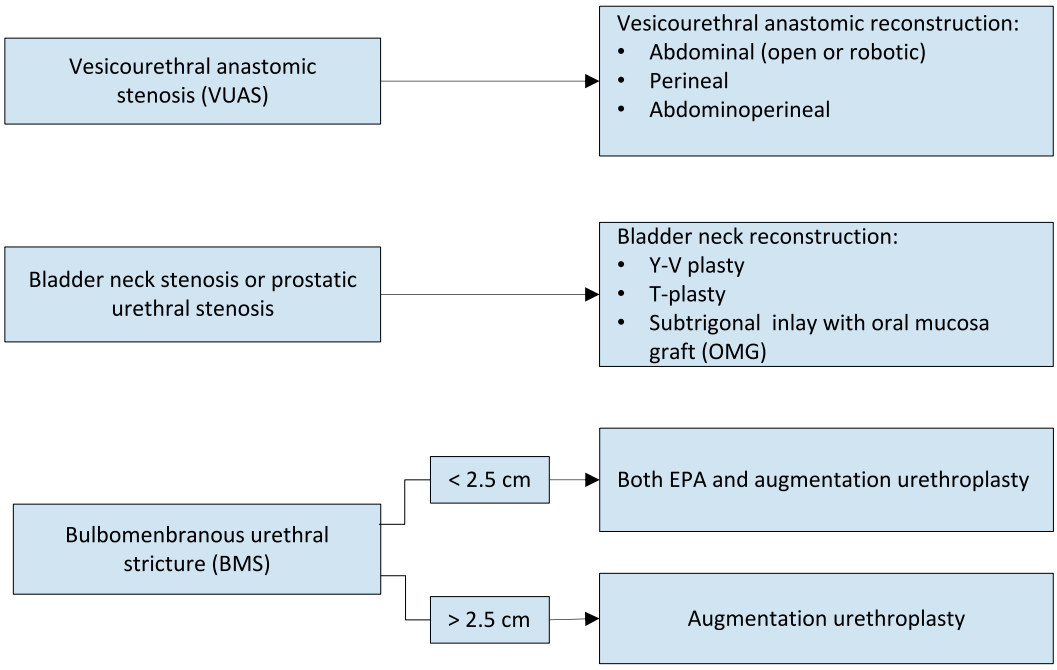
Recommendations	**Strength rating**
Perform visually controlled dilatation or direct vision internal urethrotomy (DVIU) as 1st line-treatment for a non-obliterative vesico-urethral anastomosis stricture (VUAS) or radiation-induced bulbomembranous strictures (BMS).	Weak
Do not perform deep incisions at the six and twelve o' clock position during DVIU for VUAS or radiation-induced BMS.	Strong
Perform transurethral resection (TUR) or "hot-knife" DVIU as 1st line-treatment for patients with non-obliterative bladder neck stenosis (BNS) after surgery for benign prostatic obstruction.	Strong
Perform repetitive endoluminal treatments in non-obliterative VUAS or BNS in an attempt to stabilise the stricture.	Weak
Warn patients about the risk of *de novo* urinary incontinence (UI) or exacerbation of existing UI after endoluminal treatment.	Weak

Do not perform endoluminal treatment in case of VUAS, BMS and BNS with complete obliteration.	Strong
Do not use stents for strictures at the posterior urethra.	Weak

6.3.5.1.3 Lower urinary tract reconstruction for non-traumatic posterior urethral stenosis

If endoluminal treatment (repeatedly) fails or in case of a completely obliterated posterior stenosis [406, 407, 411, 412], lower urinary tract (LUT) reconstruction may be considered in fit patients motivated to undergo surgery (Figure 6.1). The choice of LUT reconstruction will depend upon the length, location, calibre and aetiology of the stenosis, continence status, bladder function, previous radiotherapy, patient's preference, and surgeon's expertise.

Figure 6.1: Options for lower urinary tract reconstruction of non-traumatic posterior urethral obstruction (stenosis/stricture)



6.3.5.1.3.1 Redo vesico-urethral anastomosis for vesico-urethral anastomotic stenosis after radical prostatectomy

After excision of the stenosis, ReDo vesico-urethral anastomosis (ReDo VUA) can be performed. This may be performed via a retropubic, perineal, combined abdominoperineal or robot-assisted approach. Nikolavsky *et al*., proposes a retropubic approach for VUAS involving the bladder neck, a perineal approach for short VUAS with intact bladder neck and an abdominoperineal approach for long segment (> 3 cm) VUAS with bladder neck involvement [411]. The ReDo VUA must be performed in a tension-free fashion which can be achieved either by mobilisation of the bladder (retropubic approach), mobilisation of the bulbar urethra with corporal splitting and inferior pubectomy if necessary (perineal approach) or both (abdominoperineal approach) [411, 413]. Dinerman *et al*., reported a robot-assisted abdominoperineal approach in a case with 4.5 cm long complete obliteration [414]. Kirshenbaum *et al.,* reported a pure robot-assisted abdominal approach. Regardless of the approach, the procedure is technically demanding due to the location deep under the pubic symphysis, and the proximity of the external sphincter [413]. As a consequence, surgical morbidity must be considered. As most patients with VUAS were healthy enough to undergo RP, most patients will likewise remain fit and eligible for VUAS surgical reconstruction [411, 413].

Table 6.9: Outcomes of redo vesico-urethral anastomosis

Study	N	Approach (%)	Previous RT (%)	FU (months)	Length (cm)	Patency (%)	Incontinence (%)	Complications (%)
Nikolavsky *et al*. [411]	12	Perineal: 25 Abdominal: 67 Abdominoperineal: 17	25	76 (14-120)	2.5 (1-5)	67	58	Persistent extravasation due to anastomotic dehiscence grade 3b: 8.3 (prior RT)
Mundy *et al*. [413]	17	Transperineal	0	NR	NR	88	100	NR
	6		100	NR	NR	67	100	NR
Schuettfort *et al*. [415]	22	Transperineal	0	45 (4-77)	NR	91	100*	Rectal injury: 4 Lower leg paresthesia: 4
	1		100		NR	0	100*	
Pfalzgraf *et al*. [416]	20	Retropubic	NR	63 (15-109)	NR	60	65**	UTI: 5 Fever: 5 Renal failure: 5 (all grade 2)
Giudice *et al*. [417]	10	Perineal: 5 Abdominal: 4 Combined: 1	NR	30 (4-106)	NR	80	70	NR
Dinerman *et al*. [414]	1	Robot-assisted abdominoperineal	0	12	4.5	100	0***	0
Kirshenbaum *et al*. [412]	5	Robot-assisted abdominal (±VY-plasty)	0	14 (5-30-)	NR	60	0	Pubovesical fistula: 20 grade 3b

FU = follow-up; NR = not reported; RT = radiotherapy; UTI = Urinary tract infection.

* *incontinent before ReDo VUA.*

** *de novo incontinence in four out of eleven patients.*

****social continent (1 pad/day).*

ReDo VUA in non-irradiated patients yields patency rates of 60-91% (Table 6.9) [411-413, 415-417]. Prior radiotherapy is a risk factor for failure [413, 415]. In addition, radiation-induced bladder toxicity might provoke reduced bladder capacity, low bladder compliance, bladder spasms and pain, and urethral necrosis making reconstruction futile (see below) [393, 413, 418]. ReDo VUA should only be done in patients with adequate bladder function and in the absence of (peri)-urethral pathology (urethral necrosis, calcification, fistulation). Flaps (gracilis flap, peritoneal flap) to support and protect the anastomosis may be beneficial in irradiated patients [411].

With the transperineal approach, UI is inevitable, as this approach disrupts the external sphincter [412, 413, 415, 417]. With the retropubic approach, Pfalzgraf *et al*. reported *de novo* incontinence in only four out of eleven (36%) patients [416]. In the series of Nikolavsky *et al*., where a retropubic approach was predominantly used, incontinence rate was 58% [411]. Kirshenbaum *et al*., reported no incontinence in five patients treated by robot-assisted retropubic approach [412]. Giudice *et al*., reported incontinence in one out of four patients treated with the retropubic approach [417]. Therefore, some authors [101, 411, 412] have proposed a preference for the retropubic approach in patients with good pre-operative urinary continence, although both approaches have never been directly compared for UI. In addition, the lack of perineal dissection by a retropubic approach will preserve the perineal anatomy and vascularisation which makes subsequent artificial urinary sphincter (AUS) less demanding [412]. Artificial urinary sphincter implantation should be deferred because of the risk of VUAS recurrence and difficulty of treating any recurrent VUAS with the cuff of the AUS in place [397, 413]. The exact timing of AUS placement is not consensual in the literature but most advise waiting at least three to six months to ensure stability of the VUA patency [393, 410, 413, 415, 416].

Due to the complexity of this pathology the EAU Urethral Strictures Panel advises that VUAS reconstruction should be performed only in experienced high-volume centres, particularly after prior radiotherapy or other energy ablative treatments.

Summary of evidence	LE
ReDo VUA has patency rates of 60-91% in non-irradiated patients and 67% in irradiated patients with obliterative VUAS or VUAS refractory to endoluminal treatment.	3
Urinary incontinence is inevitable after transperineal ReDo VUA. Artificial urinary sphincter placement can be offered after three to six months if patency of ReDo VUA is ensured.	3
De novo incontinence with retropubic ReDo VUA is 0-58%.	3

Recommendations	Strength rating
Perform ReDo vesico-urethral anastomosis (VUA) in non-irradiated patients and irradiated patients with adequate bladder function with obliterative vesico-urethral anastomosis stricture or vesico-urethral anastomosis stricture refractory to endoluminal treatment.	Weak
Warn patient that urinary incontinence (UI) is inevitable after transperineal ReDo VUA and that subsequent anti-UI surgery might be needed in a next stage, after at least three to six months.	Strong
Offer ReDo VUA by retropubic approach if the patient is pre-operatively continent.	Weak

6.3.5.1.3.2 Posterior stenosis after surgery for benign prostatic obstruction

6.3.5.1.3.2.1 Bladder neck reconstruction for bladder neck stenosis after surgery for benign prostatic obstruction

The bladder neck is augmented by advancement of local bladder flaps (Y-V or T-plasty) with or without resection of scar tissue. They are used for BNS refractory to endoscopic treatments [412, 419-421]. Patency rates vary between 83-100% with fourteen to 45 months follow-up [412, 419-421]. There is a trend to perform bladder neck reconstruction by minimally invasive approach (laparoscopic, robot-assisted) [412, 420, 421]. *De novo* incontinence rate ranges from 0-14% [412, 419-421]. Satisfaction among patient is high with 88.5% of patients stating that they are pleased with the surgery, with an improvement of QoL in 75% of patients [419, 421]. Recently, a robot-assisted augmentation technique with subtrigonal buccal mucosa inlay has been successfully reported in a case report, but this technique requires further investigation [422].

See supplementary Table S6.14 for further information.

6.3.5.1.3.2.2 Bulbomembranous strictures after surgery for benign prostatic obstruction

Bulbomembranous urethral strictures (BMS) after TURP or simple prostatectomy are managed as bulbar strictures and can be treated by EPA or augmentation urethroplasty with a graft, taking into account the length and tightness of the stricture [84, 423]. As reconstruction is in the proximity of the external sphincter and the bladder neck was already damaged during BPO surgery, the risk of incontinence (up to 25%) is present [84].

Summary of evidence	LE
Bladder neck reconstruction with Y-V or T-plasty for treatment refractory BNS has patency rates of 83-100%.	3
Incontinence occurs in up to 14% with bladder neck reconstruction and up to 25% after reconstruction of BMS after previous surgery for BPO.	3

Recommendations	Strength rating
Perform bladder neck reconstruction with Y-V or T-plasty for treatment refractory bladder neck stenosis (BNS).	Weak
Warn patients about *de novo* urinary incontinence after reconstruction for BNS or bulbomembranous urethral strictures with previous benign prostatic obstruction surgery as aetiology.	Strong

6.3.5.1.3.3 Radiation/high-energy induced posterior strictures

6.3.5.1.3.3.1 Bulbomembranous strictures secondary to radiation/high energy sources

The major challenge in treating radiation-induced strictures is the consequent tissue damage with impaired healing capacity, involving not only the stricture itself but also the adjacent proximal and distal areas of the scar [413, 424]. Additionally, proximity of the stricture to the external sphincter can further complicate surgery [84]. Due to these challenges, patients with radiation-induced BMS have long been considered poor candidates for urethral reconstruction and have been treated with urinary diversion if endoscopic treatments failed or were not possible [413].

Most radiation-induced BMS are short and in these cases, EPA is possible [84, 189, 425, 426]. Reported patency rates vary between 67-95% [84, 189, 426, 427]. *De novo* UI was reported in 33-36% of cases [84, 189, 426, 427] and this seems to be higher compared to the rates reported for bulbar and traumatic-posterior strictures (see sections 6.3.2 and 6.3.5). Chung *et al*., reported *de novo* incontinence in twelve out of 36 (33%) patients with EPA for radiation-induced BMS vs. four out of 33 (12%) patients with EPA for PFUI (p=0.05) [427].

Excision and primary anastomosis has the advantage of avoiding the use of a graft or a local flap in an area of poor vascular health. However, EPA will not be possible for BMS with a long bulbar segment and in these cases, augmentation urethroplasty will be necessary despite the aforementioned concerns [189, 426, 428, 429]. Glass *et al*., used a cut-off of 2.5 cm to proceed with augmentation urethroplasty, whilst this was 2 cm by Meeks *et al*. [426, 429]. Some authors have even used augmentation urethroplasty as their standard technique for radiation-induced BMS [355]. Both dorsal [423, 428] and ventral onlay [355, 429] have been described to treat radiation-induced BMS. In the absence of a robust vascular graft bed, the support by a gracilis flap has been proposed during ventral onlay graft urethroplasty [429, 430]. Patency rates with augmentation urethroplasty vary between 50-83% [189, 355, 426, 428] with *de novo* incontinence ranging between 11-50% [189, 355, 428](see supplementary Table S6.15). Rourke *et al*., reported a patency rate of 91% vs. 75% for EPA and augmentation urethroplasty, respectively, but this difference did not reach statistical significance (p=0.31) [428]. Of note, strictures treated with augmentation urethroplasty were significantly longer compared to those treated by EPA (respectively 6.1 vs. 2.1 cm; $p < 0.001$). They reported no significant differences in *de novo* UI (26 vs. 25%; p=1), new onset ED (35 vs. 0%; p=0.06) or other adverse events (30% vs. 33%; p=1) [428].

6.3.5.1.3.3.2 Prostatic strictures secondary to radiation/high energy sources

Radiotherapy and high-energy modalities (cryoablation, HIFU) might provoke prostatic necrosis, sloughing and obstruction [101]. Cases refractory to TUR and with good bladder capacity might be salvaged by prostatectomy taking into account the morbidity associated with salvage RP (rectal injury, VUAS, incontinence) [101, 424]. Mundy *et al*., treated nine patients with patency in six, (67%) and one (11%) needing an AUS for severe incontinence [413].

Cases with impaired bladder function, urethral necrosis and/or peri-urethral pathology should be considered for supravesical diversion, especially if a suprapubic catheter is not tolerated due to bladder pain or spasms [393, 410, 413, 418].

Recently, a "pull-through" procedure has been reported as an alternative to cutaneous diversion for reconstruction of the devastated posterior urethra associated with a defunctionalised bladder after radiation where tissue vascularity and quality is poor [431]. This novel technique of total LUT reconstruction combines salvage cystectomy, ileal neobladder formation and urethral pull-through. An AUS was implanted in a 2nd stage. All eight patients maintained a patent posterior urethra after a median follow-up of 58 (range 16-84) months. Five patients experienced low-grade complications after the 1st stage, but no high-grade complications were reported. Four out of eight (50%) patients experienced cuff erosion with need for removal and subsequent reimplantation. After a median of two revision surgeries (range 0 to 4), all patients achieved social continence enhancing QoL [431]. This technique requires further validation before its use can be recommended.

Summary of evidence	**LE**
Patency rates with EPA and augmentation urethroplasty are respectively 67-95% and 50-83% in case of radiation-induced BMS.	3
Radiation-induced BMS longer than 2-2.5 cm are rarely amenable for EPA.	3
De novo incontinence and new onset ED after urethral surgery for radiation-induced BMS are reported in respectively 11-50% and 0-35% of cases.	3
Salvage prostatectomy can achieve patency in 67% of patients for prostatic strictures after irradiation or high-energy treatments but morbidity is substantial.	4

Recommendations	**Strength rating**
Use either excision and primary anastomosis or augmentation urethroplasty for short (< 2.5 cm) radiation-induced bulbomembranous strictures (BMS) refractory to endoscopic treatment depending on surgeon's experience.	Weak
Perform augmentation urethroplasty for long (> 2.5 cm) radiation-induced BMS.	Weak

Warn patients about the risk of *de novo* incontinence and new onset erectile dysfunction after urethroplasty for radiation-induced BMS.	Strong
Offer salvage prostatectomy in motivated and fit patients with adequate bladder function in case of a prostatic stricture due to irradiation or high-energy treatment.	Weak

6.3.5.1.4 Extirpative surgery and urinary diversion for non-traumatic posterior urethral stenosis

In complex and/or recurrent cases [411], LUT reconstruction is not possible or not indicated due to severe necrosis, calcification and significant morbidity, especially severe pain [410]. Intractable haematuria or fistulation might be other reasons to abandon the urethral outlet. Typically, the patient has a history of pelvic irradiation or high energy prostate cancer treatment and several previous attempts to achieve cure. Moreover, and equally important, any of the options used to deal with a devastated posterior urethra are dependent upon good bladder capacity, compliance and function allowing for bladder preservation as well as healthy distal ureters [393, 410]. The last resort therapeutic option is urinary diversion (continent or incontinent) with or without cystectomy [413, 418]. Different techniques have been described and the choice between them largely depends on the bladder capacity, presence of local symptoms, performance status and expectations of the patient. Cystectomy during urinary diversion is able to palliate symptoms of intractable bladder pain, spasms and haematuria which are especially prevalent after pelvic radiotherapy [432-435]. The satisfaction rate was reported to be 100% and the overwhelming majority of patients would have undergone this extirpative surgery an average of thirteen months sooner in a study of fifteen patients by Sack *et al.* [436]. In a report by Faris *et al.*, 27% of the patients also required bowel diversion due to intractable gastrointestinal morbidity, highlighting the complexity of this pathology [418].

Summary of evidence	**LE**
Urinary diversion can improve QoL in patients with a devastated LUT with a high satisfaction rate.	3
Cystectomy is able to palliate symptoms of intractable bladder pain, spasms, and haematuria.	3

Recommendations	**Strength rating**
Perform urinary diversion in recurrent or complex cases with loss of bladder capacity and/or incapacitating local symptoms.	Weak
Perform cystectomy during urinary diversion in case of intractable bladder pain, spasms and/or haematuria.	Weak

6.3.5.2 Post-traumatic posterior stenosis

The acute and early management of PFUIs is discussed in the EAU Guidelines on Urological Trauma. A non-obliterative stenosis is the result of a partial injury at the membranous urethra or occurs after unsuccessful early realignment of a partial or complete injury. An obliterative stenosis is the consequence of a complete injury with a distraction defect between the ruptured urethral ends. The gap between these ends fills up with dense fibrotic tissue [11].

The deferred management of PFUI is at earliest three months after the trauma. After that period, the pelvic haematoma has nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [437] and the patient is clinically stable and able to lie down in the lithotomy position [437, 438].

6.3.5.2.1 Endoluminal treatment for post-traumatic posterior stenosis

6.3.5.2.1.1 Endoluminal treatment as primary treatment for post-traumatic posterior stenosis

Endoluminal treatment (dilation, DVIU) of an obliterative stenosis using the cut-to-the light principle will not be successful [48] and has a risk of creating a false passage towards the bladder base or rectum [439]. For a non-obliterative, short (≤ 1.5 cm) stenosis, one attempt of endoluminal treatment (endoscopic incision or dilation) can be performed. Kulkarni *et al*., reported a 92.3% and 96.5% stricture-free rate with “cold knife” and holmium laser urethrotomy, respectively (median follow-up respectively 61 and 57 months) [440]. These results are challenged by Barbagli *et al*., who reported a 51% stricture-free rate with holmium laser urethrotomy but with no data on length of follow-up available [441]. Cai *et al.,* compared patient outcomes between bipolar plasma vaporisation and “cold knife” DVIU in 53 patients with posterior traumatic (80%) and iatrogenic (20%) urethral strictures with significantly different stricture-free rates of 81.5% vs. 53.8% at a mean follow-up of 13.9 months, respectively [442]. No severe complications were reported in either group. A statistically significant shorter operative time was found in the bipolar group [442]. Barratt *et al,.* calculated a composite stricture-free rate of 20% after all types of endoscopic treatments (but with a mix of obliterative and non-obliterative

stenoses) [48]. *De novo* UI was reported in 4% of cases [48]. Repetitive endoluminal treatments are unlikely to be curative and must be discouraged as this delays the time to definitive cure and can lead to more complications [443, 444].

6.3.5.2.1.2 Endoluminal treatment after failed urethroplasty for post-traumatic posterior stenosis
In case of a non-obliterative and short (≤ 1 cm) recurrence after failed urethroplasty, endoluminal treatment can be performed [445, 446]. Although a 1st and 2nd DVIU can be successful with a stricture-free rate of 22.9-77.3% and 0-60% respectively, three or more incisions are never successful (see supplementary Table S6.16) [445-449]. Therefore, repetitive endoluminal treatments (dilations and/or endoscopic incisions) can only be considered as a palliative option [446, 450].

Summary of evidence	**LE**
Endoluminal treatment of obliterative stenoses is not successful and may create false passages towards bladder or rectum.	3
Endoluminal treatment of short, non-obliterative, stenoses has a 20-96.5% stricture-free rate.	3
A 1st DVIU has stricture-free rates of 22.9-77.3% for a short and non-obliterative recurrence after excision and primary anastomosis.	3

Recommendations	**Strength rating**
Do not perform endoscopic treatment for an obliterative stenosis.	Strong
Perform one attempt at endoluminal treatment for a short, non-obliterative stenosis.	Weak
Do not perform more than two direct vision internal urethrotomies and/or dilatations for a short and non-obliterative recurrence after excision and primary anastomosis for a traumatic posterior stenosis if long-term urethral patency is the desired intent.	Weak

6.3.5.2.2 Urethroplasty for post-traumatic posterior stenosis
In view of the complexity and difficulty of urethroplasty and the fact that the best results are obtained with its first attempt, this surgery must be performed in high-volume centres [451-453]. It has been calculated that to achieve and maintain sufficient experience in the reconstruction of PFUI, one centre per twelve million inhabitants is sufficient (for well-resourced countries) [452].

6.3.5.2.2.1 First urethroplasty for post-traumatic posterior stenosis
6.3.5.2.2.1.1 Indication and technique of urethroplasty for post-traumatic posterior stenosis
Progressive perineal EPA is the standard treatment for an obliterative stenosis and for a non-obliterative stenosis as first attempt, or after failure of primary endoluminal treatment [48, 454].

Although both a midline and inverted U-incision are possible to gain access to the posterior urethra, a midline incision is associated with a significant reduction in trauma to the superficial perineal and posterior scrotal nerves and vessels, in the rate of surgical site infections (3.1% vs. 16.4%) and reduced length of hospitalisation [376].

A combined transpubic abdomino-perineal approach is only necessary in complicated cases such as those with associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury [439]. Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure [455]. Although also considered complex situations, iatrogenic recto-urethral fistula (after misdirected endoscopic treatment), traumatic recto-urethral fistula < 5 cm from the anus, UCF and urinoma cavity can usually be corrected by a progressive perineal approach only [439, 456].

6.3.5.2.2.1.2 Patency rate after urethroplasty for post-traumatic posterior stenosis
The overall patency rate after deferred EPA is 85.7% [48]. Complete excision of scar tissue is a strong predictor for freedom of stricture whereas number (3-5 vs. 6-7) and size (3.0 vs. 4.0 cm) of sutures are not [457]. One retrospective cohort study showed a significantly improved patency rate if dorsal anterior urethral spatulation was performed compared to ventral anterior urethral spatulation [458]. Another retrospective study showed an improved patency rate after eversion of the urethral mucosa of both urethral ends before anastomosis ("valgus urethral mucosa anastomosis") [459]. The findings of both studies have yet to be confirmed in a prospective fashion.

To preserve the antegrade arterial inflow of the bulbar urethra and reduce the surgical trauma of "classic" deferred EPA, bulbar artery sparing EPA has been described [460]. Initial patency rates vary between 88.5-100% with 20-45 months of follow-up (see supplementary Table S6.17) [460-462]. Xie *et al*., only used this technique for distraction defects less than 2.5 cm [462]. No evidence exists to date whether bulbar artery sparing EPA is superior to the "classic" EPA in terms of patency rate and potency and continence rates.

In case of a very deep location of the proximal urethral end that makes anastomotic suturing impossible, Badenoch described a pull-through technique which has a 33.3-96.5% patency rate after 43-126 months of follow-up (see supplementary Table S6.18 for further information) [440, 463, 464]. With the aim to reduce stricture recurrence, Wong *et al.,* advise a 1.5 cm segment overlap of the bulbar stump within the prostatic urethra during the pull-through technique [463]. To facilitate the suturing at the proximal part of the urethra located deep under the pubic bone, the robotic approach is under exploration but there is no evidence so far of improved outcome with this approach [465].

Patency rate in children varies between 75-89.8% (Table 6.10). The statement that EPA in children is associated with poorer results [466] cannot therefore be generally accepted [467].

Table 6.10: Outcomes of EPA in children

Study	N	Follow-up (months)	patency rate	Erectile dysfunction	Incontinence	Abdomino-perineal
Podesta *et al*. [468]	49	78 (60-264)	44 (89.8%)	3 (6.1%)	9 (18.4%)	21 (43%)
Waterloos *et al*. [469]	7	57 (8-198)	6 (85.7%)	2 (28.6%)	1 (14.3%)	1 (14.3%)
Singh *et al*. [466]	5	26 (12-42)	4 (80%)	NA	0 (0%)	0 (0%)
Singla *et al*. [470]	28	36 (3-58)	21 (75%)	-	1 (3.6%)	1 (3.6%)
Voelzke *et al*. [471]	18	13 (1-71)	16 (88.9%)	-	-	1 (5.6%)

N = number of patients; NA = not applicable.

6.3.5.2.2.1.3 Sexual function, urinary continence, and rectal injury after urethroplasty for post-traumatic posterior stenosis

Regarding erectile function, a prospective study by Hosseini *et al*., found no significant difference before, and three or six months after EPA for posterior traumatic stenosis [472]. Another prospective study by Tang *et al*., also demonstrated no significant overall change in ED after urethroplasty. However, in the subgroup of patients with pre-operative non-vascular ED, a significant post-operative increase in ED was observed [473]. A meta-analysis of retrospective studies showed a significant decline of the rate of ED from 43.27% before to 24.01% after posterior urethroplasty ($p < 0.001$) [474]. Assessment of erectile function and its definitive treatment (e.g., penile prosthesis) should be performed two years after the trauma because of the potential return of normal erectile function within that time [475, 476].

After deferred EPA, antegrade ejaculation is present in 98.3-100% of cases [477, 478]. Decreased ejaculatory volume and/or diminished ejaculatory force were reported in 17.2-18.7% of cases but it cannot be assessed whether this is due to the trauma or due to the surgery [477, 478].

Continence after PFUI and urethroplasty is generally attributed to a competent bladder neck [48]. On the other hand, as most ruptures occur at the bulbomembranous junction just below the external sphincteric mechanism, at least a part of the external sphincter mechanism can be spared during urethroplasty [479]. Therefore, incontinence is rare with deferred EPA (6.8%) and is usually due to incompetence of the bladder neck although an incompetent bladder neck will not necessarily result in incontinence after urethroplasty [48, 479].

Rectal injury is a relatively rare (0-10.2%) but severe complication after deferred EPA (see supplementary Table S6.19) [437, 449, 455, 458, 480-484]. The risk of rectal injury tends to be higher in complicated cases or cases with previous urethral manipulations [437, 480, 485].

6.3.5.2.2.2 ReDo-urethroplasty for post-traumatic posterior stenosis

In case of a recurrent stenosis, a repeat ("ReDo") urethroplasty is possible. In the majority of cases, especially if not all consecutive length-gaining manoeuvres have been used during the 1st EPA, another EPA can be performed [468, 480, 481, 486, 487]. The Badenoch pull-through technique is again an option if no adequate mucosa-to-mucosa suturing is possible (See supplementary Table S6.18) [463, 464]. In case of excessive dead space after resection of the fibrosis, gracilis muscle [485] or omental flaps (laparoscopically harvested if urethroplasty was performed using perineal approach only) [439, 483] have been advised to fill up this space

and support the anastomosis. These flaps, or alternatively bulbospongious muscle or local subcutaneous dartos flaps, are also useful to separate the suture lines in case of a concomitant recto-urethral fistula [439, 451, 456, 485]. If the urethra cannot be anastomosed in a tension-free fashion, despite the aforementioned manoeuvres, or in cases of ischemic narrowing/necrosis of the bulbar urethra, options are a tubed preputial island flap, staged BMG urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty [451, 481, 486, 488]. In case of entero-urethroplasty, the sigmoid colon is preferred above ileum (which is in turn better than stomach) because of the proximity of the vascular pedicle to the perineum. Entero-urethroplasty should only be done in the presence of a competent bladder neck because subsequent implantation of an AUS is nearly impossible [488].

Patency rate of different types of ReDo-urethroplasty varies between 37.5-100% (Table 6.11) [446, 451, 453, 480, 481, 483, 486-488]. An alternative is to abandon the normal urinary outlet and opt for Mitrofanoff-vesicostomy, PU (if local perineoscrotal skin is suitable) or permanent suprapubic diversion [481, 488].

Table 6.11: Outcome of different types of ReDo-urethroplasty

Study	Type	N	Follow-up (months)	Patency rate
Bhagat *et al*. [486]	Progressive perineal EPA	28	29 (12-108)	36 (83,72%)
	Transpubic EPA	12		
	Tubed preputial flap	1		
	Staged BMG + local flap	2		
Fu *et al*. [480]	Progressive perineal EPA	55	36 (18-47)	33 (60%)
Garg *et al*. [481]	Progressive perineal EPA	40	31 ± 11	30 (75%)
	Transpubic EPA	2	25	2 (100%)
	Tubed preputial flap	1	25	1 (100%)
	Staged BMG + local flap	2	17	1 (50%)
	Radial forearm free flap	1	15	1 (100%)
Gupta *et al*. [487]	Progressive perineal EPA	52	54 (10-144)	42 (80.8%)
Koraitim M. [446]	Progressive perineal EPA	4	168 (12-300)	4 (100%)
	Transpubic EPA	5		5 (100%)
Kulkarni *et al*. [483]	Progressive perineal EPA	15	18 (6-24)	14 (93.3%)
Kulkarni *et al*. [451]	Progressive perineal EPA	541	68 (12-240)	412 (79.1%)
	Tubed preputial flap	37		30 (81%)
	Staged BMG flap	10		6 (60%)
	Staged BMG + local flap	15		13 (86.6%)
	Entero-urethroplasty	2		2 (100%)
	Radial forearm free flap	3		3 (100%)
	Pedicled anterolateral thigh flap	1		1 (100%)
Mundy *et al*. [488]	Entero-urethroplasty	11	NA	7 (63.6%)
Podesta *et al*. [468]	Transpubic EPA	4	120 (72-204)	4 (100%)
Singh *et al*. [453]	Progressive perineal EPA	8	31 (13-90)	3 (37.5%)
Singh *et al*. [466]	Progressive perineal EPA	37	26 (12-42)	32 (86.5%)
Singla *et al*. [470]	Progressive perineal EPA	1	NA	1 (100%)
	Tubed preputial flap	2	NA	2 (100%)

BMG = buccal mucosa graft; EPA = excision and primary anastomosis; N = number of patients; NA = not applicable.

Summary of evidence	LE
The best results are obtained after the 1st urethroplasty.	4
The overall stricture-free rate after EPA is 85.7%. By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed.	3
After failed endoluminal treatment, EPA is the standard treatment for a non-obliterative stenosis.	3
Both a midline and inverted U perineal incision equally gain access to the posterior urethra, but a midline incision is associated with less anatomical damage to local vessels and nerves, reduced risk of surgical site infection and hospital stay.	2b

Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure.	4
By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed except for very long distraction defects and in case of complicated situations, which include associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	3
If the urethra cannot be anastomosed in a tension-free fashion or in case of ischaemic narrowing/ necrosis of the bulbar urethra, options are a tubed preputial island flap, staged buccal mucosa graft urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty.	3
In case of excessive dead space after resection of the fibrosis, local flaps have been advised to fill up this space and support the anastomosis. These flaps are also useful to separate the suture lines in case of a concomitant recto-urethral fistula.	3

Recommendations	**Strength rating**
Perform open reconstruction for post-traumatic posterior stenosis only in high-volume centres.	Weak
Perform progressive perineal excision and primary anastomosis (EPA) for obliterative stenosis.	Strong
Perform progressive perineal EPA for non-obliterative stenosis after failed endoluminal treatment.	Strong
Perform a midline perineal incision to gain access to the posterior urethra.	Strong
Do not perform total pubectomy during abdomino-perineal reconstruction.	Strong
Reserve abdomino-perineal reconstruction for complicated situations including very long distraction defect, para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	Weak
Perform another urethroplasty after 1st failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion.	Weak
Use a local tissue flap to fill up excessive dead space or after correction of a concomitant recto-urethral fistula.	Weak

7. DISEASE MANAGEMENT IN FEMALES

7.1 Signs and symptoms of female urethral strictures

The symptoms of female urethral strictures are non-specific and therefore generally non-diagnostic. Female urethral stricture presents with mixed filling and voiding symptoms with frequency in 60.2%, urgency in 51%, poor flow in 42%, incomplete emptying in 42%, UI in 36% (stress, urge or mixed), nocturia in 26%, UTI in 20% and straining to void in 16%. It very rarely presents with urethral pain (3%), terminal dribble (1%), haematuria (1%) or renal failure (1%) (see supplementary Table S7.1) [15, 23, 124, 126, 127, 132, 134, 136, 138, 489-492]. There is often a significant delay in diagnosis of FUS from time of development of symptoms with mean delays of 4.3-12 years described (range 1-30 years) [129, 136].

7.2 Diagnosis of female urethral strictures

Twenty-four studies detail investigations leading to a diagnosis of FUS (see supplementary Table S7.2) [13, 15, 124-127, 130-136, 138, 491-500]. In all cases a full history was taken, and a detailed pelvic examination was performed to assess for prolapse, masses, scars and vulval dermatological disorders such as LS, lichen planus or vulvo-vaginal atrophy. Flow rate and US PVR assessment was evaluated in eighteen (75%) and seventeen (71%) studies, respectively. Lateral VCUG was performed routinely in fifteen studies (63%) and as required in one study (4%). Cystourethroscopy was performed routinely in thirteen studies (54%) and as required in two studies (8%). Urodynamics (UDS) were performed routinely in four studies (17%) and as required in seven studies (30%) whilst video-urodynamics (VUDS) were performed routinely in three studies (13%) and urethral calibration (to < 14 Fr) also in three studies (13%). Pelvic MRI was performed as required in four series (17%) whilst transrectal US (TRUS) and renal US were each performed routinely in two series (8%) and intravenous urography (IVU) in ten (4%).

Flow rate and PVR assessment make inherent sense as initial non-invasive screening tools and allow for simple monitoring of effect of treatment. Voiding cystourethrography and/or VUDS will permit diagnosis of BOO [23, 499], visualisation of ballooning above the proximal end of the FUS [134], and delineation of alternate or co-existent diagnoses such as detrusor overactivity (DO) and SUI [127], although VCUG, VUDS and UDS require the ability to insert a 6 Fr catheter and may not be possible without preliminary urethral dilatation in all cases of FUS [492]. Likewise, passage of a cystourethroscopy will require a preliminary dilation in the majority of cases even when a paediatric uretero-renoscope is utilised [125]. Cystourethroscopy will allow for formal identification of the distal end of the FUS and will also allow for exclusion of a functional cause of BOO [134]. Magnetic resonance imaging is performed mainly to exclude alternate pathology such as urethral diverticulum and urethral carcinoma and also allows assessment of the degree of urethral fibrosis associated with FUS [492, 501]. Proponents of TRUS utilise it in lieu of MRI and for visualisation of the dilated urethra above the proximal end of the FUS [502].

7.3 Treatment of female urethral strictures

7.3.1 ***Minimally invasive techniques for treatment of female urethral strictures***

Several minimally invasive treatments have been reported; these include urethrotomy, dilatation, meatotomy and meatoplasty. Meatotomy and meatoplasty are essentially the same procedure in the female urethra and the term 'meatoplasty' will be used throughout this document.

7.3.1.1 Urethrotomy for treatment of female urethral strictures

No papers were found detailing the use and outcomes of urethrotomy specifically for the management of FUS. Internal urethrotomy or dilation was used by Massey and Abrams [503] to treat a variety of pathologies, including FUS, causing symptoms of obstructed voiding, and resulted in symptomatic improvement in 80% of patients. As this study included women with a variety of complaints and did not assess urodynamic parameters, the results in the patient subset with true urethral stricture are unclear. If utilised, urethrotomy in the female urethra involves incisions at three, nine and occasionally twelve o'clock [503].

7.3.1.2 Urethral dilatation for treatment of female urethral strictures

With this treatment, the urethra is dilated to between 30 Fr and 41 Fr Some patients will continue with ISD. Romman *et al*., 2012 [491] and Popat & Zimmern [492] also described suture plication of bleeding areas of the meatus if required post-urethral dilatation.

Four studies described the results after twelve to 59 months follow-up of, in total, 183 patients having dilatation only. Patency rates ranges from 7.5-51% (see Table 7.1) [127, 128, 491, 492]. In another four studies that included, in total, 31 patients that continued to perform ISD, stabilisation of the stricture with "patency" was obtained in 37.3-100% of cases at twelve to 21 months of follow-up (see Table 7.1) [13, 132, 135, 497].

New onset SUI (0.8%) and other complications are very rare after dilation (see supplementary Table S7.3). Due to the low complication rate, the minimally invasive nature of the technique and the reasonable success rate, it is acceptable to start with urethral dilation as a first-line treatment for an uncomplicated FUS.

7.3.1.3 Meatoplasty for treatment of female urethral strictures

Meatal stenosis is extremely rare, with only 2/58 (3%) of females evaluated for voiding dysfunction found to have true meatal stenosis [504]. Only three meatoplasty papers were identified containing 60 patients (see supplementary Table S7.4): one [505] detailed meatoplasty outcomes in a series of 58 girls whilst the 2nd was from a study analysing outcomes of various forms of FUS treatment that included one case of meatoplasty [506], and the third was a case report [132]. The patency rate of meatoplasty in girls is excellent with 97% of the 58 girls in Hesing's series having a successful outcome with no reported side effects at twelve months. Forty-eight of 50 patients experienced resolution of their recurrent UTIs and improved voiding symptoms one year after meatoplasty [505]. None of these studies reported incontinence or other acute complications. For short meatal strictures, meatoplasty is the first-line treatment option.

7.3.2 ***Urethroplasty for treatment of female urethral strictures***

Twenty-five papers report the outcomes of urethroplasty for FUS disease in 231 patients in total after the scope search of the Panel. The Panel have analysed the outcomes of these urethroplasty according to flap or graft type as: vaginal graft, vaginal flap, labial/vestibular graft, labial/vestibular flap and buccal or lingual graft.

In female urethroplasty, a dorsal approach is via a stricturotomy at twelve o'clock, a ventral approach is via a stricturotomy at six o'clock and circumferential is a full circumference reconstruction.

7.3.2.1 Vaginal graft augmentation urethroplasty for treatment of female urethral strictures

There were four studies reporting vaginal graft urethroplasty including 37 patients [15, 495, 500, 507]. All

37 vaginal graft urethroplasties were performed via a dorsal approach in women with a mean/median age of 47.5-60.6 years (range 35-70). In these studies, patency rates of 73-100% were reported after 22-27 months follow-up (Table 7.1). No complications and no new onset UI were reported.

See supplementary Table S7.5 for further information.

7.3.2.2 Vaginal flap augmentation urethroplasty for treatment of female urethral strictures

Vaginal flap urethroplasty was reported in 70 women and was always via a ventral approach, utilising an inverted U vaginal flap inlay in five studies (n=52) [126, 127, 130, 489, 490], a lateral C vaginal flap in three studies (n=17) [124, 132, 136] and one vaginal island flap urethroplasty in one patient [130]. At a mean/median follow-up time of 30-80.7 months, patency rates of 67-100% were reported (Table 7.1). Eight (11.4%) patients had a simultaneous pubo-vaginal sling (PVS), four (5.7%) had a simultaneous Martius fat pad flap interposition and one (1.4%) had a simultaneous excision of urethral diverticulum. Five (7.1%) patients developed new onset UI, two (2.9%) developed UTIs and two (2.9%) described temporary intravaginal direction of their urinary stream.

See supplementary Table S7.6 for further information.

7.3.2.3 Labial/vestibular graft augmentation urethroplasty for treatment of female urethral strictures

There were four papers detailing the outcomes of 31 patients having labial or vestibular graft urethroplasty (see supplementary Table S7.7); nineteen had ventral labial minora graft [131, 138, 494] and twelve had dorsal labial graft [135]. At a mean follow-up of fifteen to 24 months, patency rates of 75-100% were reported with ventral grafting whilst this was 100% with dorsal grafting at six to fifteen months follow-up (Table 7.1). One (5.2%) ventral graft patient developed a UTI post-surgery. There were no other complications (including UI).

7.3.2.4 Labial/vestibular flap urethroplasty for treatment of female urethral strictures

There were two papers detailing the outcomes of nineteen patients having labial/vestibular flap urethroplasty: two had a ventral labia minora flap [508] and seventeen had a dorsal vestibular flap [16]. At a follow-up of 24 months the two ventral flap patients (100%) remained stricture-free whilst fifteen (88%) dorsal flap patients remained stricture-free at a mean of twelve months follow-up (Table 7.1 and supplementary Table S7.8). There were no adverse short- or long-term effects reported in either group.

7.3.2.5 Buccal and lingual mucosal graft augmentation urethroplasty for treatment of female urethral strictures

There were twelve papers detailing the outcomes of 73 patients, all treated with BMG except in the series of Sharma *et al.,* who used lingual mucosa graft (LMG) in fifteen patients at the dorsal urethra [125]; 44 patients with dorsal onlay oral (buccal or lingual) mucosa graft (DOOMG) [125-127, 130, 133, 493, 499, 507, 509]; 27 with ventral onlay BMG (VOBMG) [126, 134, 510, 511] and two with circumferential BMG urethroplasty [126]. At a mean/median follow-up of six to 28 months, 62.5-100% of DOOMG urethroplasty patients were stricture-free whilst 50-100% of VOBMG patients were stricture-free at a mean of ten to 24 months follow-up. Both circumferential BMG patients were stricture-free at a mean of 21 months follow-up (Table 7.1). Seven (15.9%) DOOMG patients suffered a low-grade short-term adverse effect and no patients in any subgroup developed sustained new onset UI.

For further information see supplementary Tables S7.9, S7.10 and S7.11.

7.3.2.6 Anastomotic urethroplasty

Anastomotic urethroplasty has only been described in two cases in the literature – both in women with very short mid-urethral stricture and both of whom were stricture-free at four and 24-months follow-up respectively. None of them suffered from UI post-operatively [126, 496] (see supplementary Table S7.12).

Table 7.1: Summary of available evidence on treatment of female urethral strictures

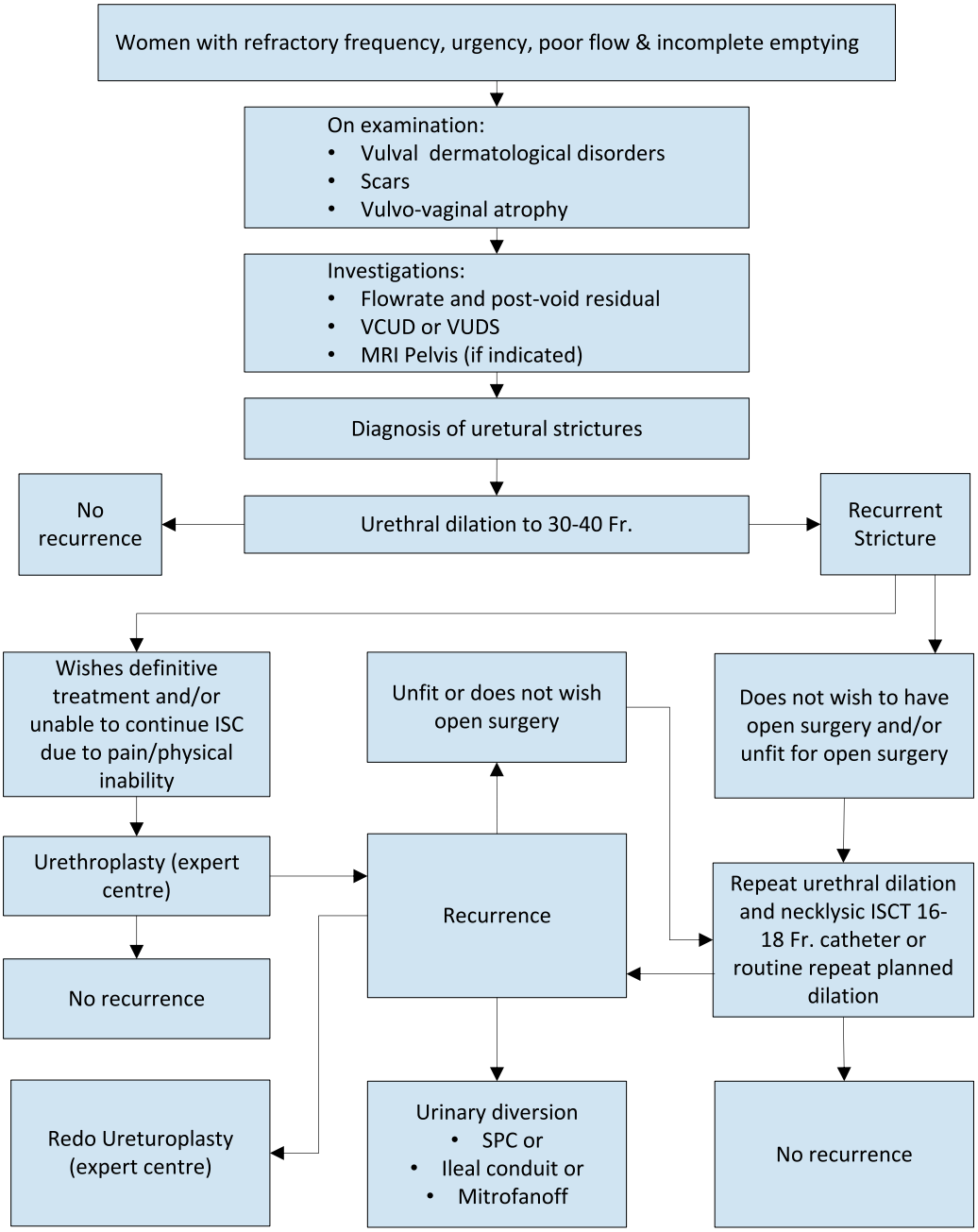
Treatment	No. of studies	N	Patency rate (%)	UI (%)	Mean/Median FU Months	Refs
Urethral Dilatation	4	183	7.5-51	0	12-59	[127, 128, 491, 492]
Urethral Dilatation + ISD/ planned repeat dilatation	4	31	37.3-100	1.9	12-21	[13, 132, 135, 497]
Dorsal Vaginal graft urethroplasty	4	37	73-100	0	22.4-27	[15, 495, 500, 507]
Ventral Vaginal flap urethroplasty	8	70	67-100	7	30-80.7	[124, 126, 127, 130, 132, 136, 489, 490]
Ventral Labial/Vestibular graft urethroplasty	3	19	75-100	0	15-24	[131, 138, 494]
Dorsal Labial/Vestibular graft urethroplasty	1	12	100	0	6-15	[135]
Ventral Labial/Vestibular flap urethroplasty	1	2	100	0	24	[508]
Dorsal Labial/ Vestibular flap urethroplasty	1	15	88	0	12	[16]
Dorsal BMG urethroplasty	9	44	62.5-100	0	6-28	[125-127, 130, 133, 493, 499, 507, 509]
Ventral BMG urethroplasty	4	27	50-100	0	10-24	[126, 134, 510, 511]

FU = follow-up; ISD = intermittent self-dilatation; N = number of patients; UI= urinary incontinence.

Summary of evidence	LE
Female urethral stricture symptoms are long standing and non-specific, the most commonly reported are frequency, urgency, poor flow, incomplete emptying, and UI. It is important to exclude FUS in female patients with LUTS.	3
Urethral dilatation alone to 30-41 Fr provides low stricture-free rates of mean 35% at mean follow-up 36.3 months.	3
Urethral dilatation and ISC or planned repeat dilatation provides stricture-free rates of 75%.	3
Urethroplasty provides stricture-free rates of 81-92%. No one particular type of urethroplasty is superior to another.	3
Meatotomy/meatoplasty for short meatal strictures has a success rate of 95% at twelve months follow-up.	3

Recommendations	Strength rating
Perform flow rate, post-void residual and voiding cystourethrogram or video-urodynamics in all women with refractory lower urinary tract symptoms.	Strong
Perform urethral dilatation to 30-41 Fr as initial treatment of female urethral stricture (FUS).	Weak
Perform repeat urethral dilatation and start planned weekly intermittent self-dilatation (ISD) with a 16-18 Fr catheter for the 1st recurrence of FUS.	Weak
Perform urethroplasty in women with a 2nd recurrence of FUS and who cannot perform ISD or wish definitive treatment. The technique for urethroplasty should be determined by the surgeon's experience, availability and quality of graft/flap material and quality of the ventral vs. dorsal urethra.	Strong
Treat meatal strictures by meatotomy/meatoplasty.	Weak

Figure 7.1: Women with refractory frequency, urgency, poor flow and incomplete emptying


Women with refractory frequency, urgency, poor flow & incomplete emptying
On examination:
• Vulval dermatological disorders
• Scars
• Vulvo-vaginal atrophy
Investigations:
• Flowrate and post-void residual
• VCUD or VUDS
• MRI Pelvis (if indicated)
Diagnosis of uretural strictures
No recurrence
Urethral dilation to 30-40 Fr.
Recurrent Stricture
Wishes definitive treatment and/or unable to continue ISC due to pain/physical inability
Unfit or does not wish open surgery
Does not wish to have open surgery and/or unfit for open surgery
Urethroplasty (expert centre)
Recurrence
Repeat urethral dilation and necklysic ISCT 16-18 Fr. catheter or routine repeat planned dilation
No recurrence
Redo Ureturoplasty (expert centre)
Urinary diversion
• SPC or
• Ileal conduit or
• Mitrofanoff
No recurrence

ISC = intermittent self-catheterisation; MRI = magnetic resonance imaging; VUDS = video-urodynamics.

8. DISEASE MANAGEMENT IN TRANSGENDER PATIENTS

8.1 Treatment of strictures in trans men

In trans men, stricture treatment depends on the time after neophallic reconstruction, stricture location, stricture length and quality of local tissues [512].

8.1.1 Management of strictures early after neophallic reconstruction

Urethral surgery on tissues in the acute phase of inflammation and wound healing is not indicated and should be postponed until any healing problems of the neophallus have been resolved and scar tissue formation in the urethra has been stabilised. This usually takes six months [32, 145]. Endoscopic incision for short (< 3 cm)

urethral strictures has been performed, mainly at the anastomotic site, with a maximum stricture-free rate of only 16.7% when performed within six months after neophallic reconstruction [513]. Insertion of a suprapubic catheter is the first-line treatment in cases of obstructive symptoms severely affecting the patient's QoL, recurrent UTI or retention. The alternative is perineostomy, which is a specialist procedure and should be performed by a urologist familiar with transgender urethral anatomy. The perineostomy may be closed at the time of formal urethral reconstruction [145].

*8.1.2 **Treatment of meatal stenosis in trans men***

Intermittent urethral dilatation is an option, as palliative treatment, for low-grade meatal stenosis with the interval of dilatation depending on the interval of stricture recurrence. Patients with high-grade meatal stenosis, those who refuse ISD, or those who want a durable solution should be offered simple meatotomy. Patency is 75% (mean follow-up 39 months) but the drawback is that the meatus will be in a hypospadiac position [145]. Alternatively, a staged urethroplasty can be offered [145].

*8.1.3 **Treatment of strictures at the neophallic urethra***

Endoscopic incision of a short stricture at the neophallic urethra has been reported but evidence is very scarce, and the long-term results seem to be disappointing (34% patency rate after median follow-up of 51 months) [513].

Single-stage graft urethroplasty is only possible if the graft can be supported and covered by the healthy surrounding fatty tissue of the neophallus. Experience is very limited and reported patency rate is 50% after a mean follow-up of 102 months [145].

The standard treatment for these strictures is staged urethroplasty with or without graft augmentation [145, 512] (BMG or full thickness SG) [32, 145]. A patency rate of 69.7% has been described with these techniques (mean follow-up: 25 months) [145].

For complex (e.g., fully obliterated) or recurrent strictures at the neophallic urethra, a complete urethral substitution of this part needs to be performed. Different suitable flaps have been described (radial forearm free flap, superficial circumflex iliac artery free flap, pedicled groin flap). Double-face grafts with the ventral graft supported by rotating a part of the neoscrotum or by a gracilis flap have been successfully reported in a very limited number of patients [512].

*8.1.4 **Treatment of strictures at the anastomosis neophallic urethra-fixed part of the urethra***

Short, non-obliterative, strictures can be treated by endoscopic incision. A first endoscopic incision has a 45.5% patency rate, but this dropped to 0% in case of three or more attempts (median follow-up of 51 months) [513]. Therefore, repetitive endoscopic incisions should be discouraged unless with palliative intent.

For very short (< 1 cm) low-grade strictures, Heineke-Mikulicz urethroplasty is an option reporting a 57.9% patency rate after a mean follow-up of 44 months [145].

If endoscopic incision fails or if the stricture is nearly or completely obliterative, options are EPA or graft augmentation urethroplasty. In case of short (< 2-3 cm) strictures, EPA yields a 57.1% patency rate (mean follow-up of 35 months) [32, 145]. If EPA is not possible, usually for strictures longer than 2 cm, a ventral onlay BMG urethroplasty demonstrated a 50% patency rate (median follow-up of 9.5 months) [514]. In case of insufficient ventral tissue during graft urethroplasty, it is advised to support this graft by a local fasciocutaneous flap [515]. An alternative (especially after failure of the previous techniques) can be a staged approach, but no data are currently available [514].

*8.1.5 **Treatment of strictures at the fixed part of the urethr**a*

This part of the urethra has a more reliable blood supply, and the dorsal part of the urethra is supported by the corporal bodies of the clitoris. Therefore, single-stage dorsal inlay graft urethroplasty is possible for strictures at this site. Experience however is very limited [145, 512].

Staged repair with or without a dorsal graft is a reliable treatment for these rare strictures [145].

*8.1.6 **Definitive perineostomy in trans men***

The vast majority of trans men have a strong desire to void in a standing position [512]. Therefore, definitive perineostomy should only be offered to those with refractory strictures or to patients with strictures who do not wish to have complex reconstructive surgery [32, 145].

8.2 Peri-operative care after treatment of strictures in trans men

Anecdotally, after endoscopic incision and urethroplasty, the urethral catheter is maintained for two to three weeks [513, 514]. Peri-catheter urethrography is advised before catheter removal as it might be challenging to reinsert the urethral catheter in case of urinary extravasation [514].

8.3 Strictures in trans women

It is acceptable to start with dilation of a short and non-obliterative stricture in trans women although no long-term data about the effectiveness are available [33, 516]. If this is not possible or if it fails, a short (< 1 cm) meatal stricture can be treated by Y-V meatoplasty with an 85% stricture-free rate [517]. Somewhat longer (1-2 cm) meatal strictures can be treated by a neovaginal advancement flap (inverted U or "7-flap") with no recurrence observed after 37 months median follow-up [518].

Summary of evidence	LE
After neophallic reconstruction, local tissues go through the different stages of wound healing and stable wound healing is usually achieved after six months.	3
After two attempts, endoscopic incision is no longer successful in trans men.	3
Two-stage urethroplasty for strictures at the neophallic urethra has a stricture-free rate of 69.7%.	3
Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women has a stricture-free rate of 85%.	3

Recommendations	Strength rating
Do not perform endoscopic incision or urethroplasty within six months after neophalloplasty.	Strong
Do not perform more than two endoscopic incisions for strictures in trans men unless with palliative intent.	Strong
Perform staged urethroplasty for strictures at the neophallic urethra if open reconstruction is indicated.	Weak
Perform Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women if open reconstruction is indicated.	Weak

9. TISSUE TRANSFER

9.1 Comparison of grafts with flaps

One small RCT (LS excluded) comparing OMG with PSF found no significant difference in urethral patency rate [519]. Penile skin flaps had a higher urogenital morbidity (superficial penile skin necrosis, penile torsion, penile hypoesthesia, and post-void dribbling) and longer operation time compared to OMG. Furthermore, patient dissatisfaction was significantly higher with penile flaps [519]. Another small RCT (LS excluded) comparing penile skin grafts with PSF confirmed these findings with longer operation time and more superficial penile skin necrosis in the group of the flaps whereas the urethral patency rate was similar between both groups [362]. Several retrospective series also found a comparable urethral patency rate between PSF and grafts [273, 275, 280, 520] (Table 9.1).

Table 9.1: Comparative studies of grafts vs. flaps used in urethroplasty for anterior urethral strictures

Study	Type of study	LS	Follow-up (months)	Flap		Graft		p-value*
				Type	Urethral patency	type	Urethral patency	
Barbagli *et al*. [273]	Retrospective	Excl.	55	LIF	12/18 (67%)	OMG/PSG	36/45 (80%)	0.32
Dubey *et al*. [519]	RCT	Excl.	22-24	LIF	22/26 (84.6%)	BMG	24/27 (88.9%)	0.70
Fu *et al*. [275]	Retrospective	Excl.	>12	All types	166/199 (83.4%)	LMG	80/94 (85.1%)	0.71
Hussein *et al*. [362]	RCT	Excl.	36	TIF	15/19 (78.9%)	PSG	13/18 (72.2%)	0.25
Lumen *et al*. [280]	Retrospective	NR	42-43	All types	23/29 (79.3%)	OMG/PSG	63/75 (84%)	0.57

Sa *et al*. [520]	Retrospective	Excl.	28 (18-60)	TIF	28/34 (82.3%)	BMG	67/82 (81.7%)	0.851

BMG = buccal mucosa graft; Excl. = excluded; LIF = longitudinal island flap; LMG = lingual mucosa graft; LS = lichen sclerosus; mo = months; NR = not reported; OMG = oral mucosa graft; PSG = penile skin graft; TIF = transverse island flap; RCT = randomized controlled trial.
** if not reported: recalculated by EAU Urethral Strictures Panel with chi²-statistics.*

Due to their robust vascular pedicle, flaps can be used as a tube as well as a patch in a single-stage approach [451]. Castagnetti *et al*., showed that grafts used as a tube have significantly higher complication rates as compared to onlay grafts (OR: 5.86; 95% CI: 1.5-23.4) [521]. A review by Patterson *et al*., also reported high (circa 50%) complication and recurrence rates for tubularised grafts [522]. Iqbal *et al*., have shown an encouraging 87% stricture-free rate in 23 patients who were offered single-stage circumferential skin flap urethroplasty [284]. Therefore, if there is a need to reconstruct a complete urethral segment with a tissue-transfer tube in a one-stage operation, flaps are usually the preferred option. As flaps carry their own vascular supply to the reconstruction site, they do not rely on the local vascularisation of the recipient site. Therefore, they need to be considered in case of poor urethral vascularisation (e.g., after irradiation or dense scarring after previous urethroplasty) [280, 523]. In addition, flaps survive well in the presence of active urinary infection [524].

Grafts and flaps should not be considered competitors in urethral surgery. A combination of a flap with a graft is possible for complex, multifocal or penobulbar strictures [280, 525, 526].

Summary of evidence	**LE**
Flaps have a higher urogenital morbidity, but a comparable patency rate compared to grafts.	1b
Grafts have a significantly higher complication rate compared to flaps when complete tubularisation in a single-stage approach is needed.	1b
Flaps do not rely on the local vascularisation of the recipient site.	3

Recommendations	**Strength rating**
Use a graft above a flap when both options are equally indicated.	Strong
Do not use grafts in a tubularised fashion in a single-stage approach.	Strong
Use flaps in case of poor vascularisation of the urethral bed.	Weak

9.2 Comparison of different types of flaps

Different local flaps have been described. Penile skin flaps are generally hairless, although the ventral penile skin can be hair-bearing around the raphe in some ethnic groups/phenotypes. They can be harvested as a transverse preputial skin flap [527], a transverse distal PSF [365, 524, 528, 529] or as a longitudinal island flap [530]. Urethral patency rates vary between 74.2-100% [275, 365, 524, 527-530]. Complications include skin necrosis (0-3.8%), fistula (0-7%), penile deformity (0-7%), post-void dribbling (0-79%) and sacculation (0-16.5%) (see supplementary Table S9.1). As there are no direct comparative series available about these flaps it is not possible to determine which performs better.

Hair-bearing perineal and scrotal flaps have been described as well. Fu *et al*., demonstrated that PSF had a significantly better urethral patency rate compared to scrotal and perineal skin flaps (respectively 87.7%, 69% and 66.7%) [275]. The hair-bearing perineal and scrotal skin flaps are associated with hairball formation and chronic infection which may cause failure of the repair. A study of Blandy with long-term follow-up, reports 3% revision for calculi and 3% revision for diverticula [531].

An alternative is to epilate the needed scrotal skin prior to tissue transfer [532, 533] or to patch an OMG to the underlying dartos tissue of the scrotum after incision of the scrotal skin and use this patch as a flap in a second attempt [451].

Summary of evidence	**LE**
Hair-bearing flaps have a lower urethral patency rate compared to non-hair-bearing flaps.	3

Recommendation	**Strength rating**
Do not use hair-bearing perineal or scrotal flaps unless no other option is feasible.	Strong

9.3 Comparison of different types of grafts

Buccal mucosa is at present the most commonly used graft. Urethral patency rates of buccal mucosa vary between 75.6% and 91.7% with 16-75 months of follow-up (see supplementary Table S9.2) [534-540].

Penile skin is another popular graft, especially in uncircumcised men where the foreskin is an abundant source of graft material.

In case of LS, Trivedi *et al*., demonstrated a significantly higher urethral patency rate when using non-genital mucosal grafts for reconstruction (82.6%) compared to genital skin grafts (4%) [541]; therefore, the use of genital skin in LS cases is not indicated.

There is no RCT comparing buccal mucosa with penile skin. A secondary analysis of a meta-analysis comparing dorsal with ventral onlay graft urethroplasty found a superior urethral patency rate for buccal mucosa compared to penile skin (88.1% vs. 79%; $p < 0.001$). In this secondary analysis, no data were available about the stricture aetiology, stricture length, follow-up duration or other potential confounders between both groups [542]. A pooled analysis of non-RCTs comparing buccal mucosa (n=483) with penile skin (n=428) found a better urethral patency rate for buccal mucosa (respectively 85.9% vs. 81.8%). However, the results might be biased because of the longer follow-up time and longer stricture length in the penile skin group [543]. Lengthy skin grafts (up to 20 cm) can be taken from the foreskin in a spiroid fashion which is clearly more difficult with OMG.

The main disadvantage of BMG harvesting is the oral morbidity and because of this morbidity, lingual mucosa has been proposed as alternative. A SR and meta-analysis of comparative studies comparing LMG with BMG (four prospective, two retrospective studies) showed no significant differences in urethral patency rate and overall long-term complication rate [544-546]. These studies revealed that LMG was associated with more difficulties in eating/drinking, speaking, tongue protrusion and dysgeusia [544, 545]. In 13.8-20%, speaking problems remained after six months [544, 545]. A retrospective study of Xu *et al*., reported difficulties in tongue movements, numbness over the donor site and speaking difficulties in 6.2%, 4.9% and 2.5% of patients, respectively after twelve months [303]. On the other hand, BMG harvesting provoked more oral tightness which was present in up to 24% of patients after six months [544, 545]. Chauhan *et al*., showed that immediate and early donor site complications were more common in the BMG group, except for bleeding being more common in the LMG group. Numbness (61%), difficulty in chewing (54%), swelling (48%) and articulation (40%) were the most common problems during the first week. Late donor site complications were rare [547]. Pal *et al*., describes more short-term complications (difficulty in tongue movement and slurring of speech) in the LMG group, compared to the BMG group. Long-term complications (after three months) at the donor site (persistent pain, perioral numbness, tightness of mouth, salivary disturbance, scarring of the cheeks) were only seen in the BMG group [548]. For long strictures, buccal mucosa can be combined with lingual mucosa [303].

The use of lower lip mucosa was described, especially when smaller grafts are needed, and has similar qualities to lingual mucosa. However, a narrative review based on the experience from retrospective series showed that these grafts have a higher post-operative donor site morbidity and can lead to permanent sequelae (persistent discomfort, neurosensory deficits, salivary flow changes and important aesthetic changes) at the donor site, which have not been described with lingual mucosa [549].

Beyond the oral mucosa and penile skin graft, a multitude of other autologous grafts have been described. These include: postauricular skin [526, 550], abdominal skin [367], split-thickness mesh graft from the thigh [351], inguinal skin [302] and colonic mucosa [551] (Table 9.2). Manoj *et al.,* only used the postauricular skin when both genital skin and oral mucosa were not usable [550]. Marchal *et al.,* used postauricular skin in addition to oral mucosa to reconstruct lengthy strictures [526]. Meeks *et al.,* reported the use of abdominal skin graft mainly in patients with lengthy strictures where OMG harvesting would be insufficient, in case of prior OMG urethroplasty or if OMG was refused by the patient [367]. Pfalzgraf *et al.,* reported a comparable urethral patency rate for split-thickness mesh graft and BMG (respectively 84 and 83%), but more penile deviation (9% vs. 0%) and lower satisfaction (83.3% vs. 96.7%) with split-thickness mesh graft [351]. Xu *et al*., used colonic mucosa for lengthy (> 10 cm) strictures. Urethral patency rate was 85.7% but graft harvest requires an abdominal procedure, and 1/35 (2.9%) patient developed a colonic-abdominal fistula [551]. Due to the limited experience with grafts other than oral mucosa and penile skin, they should only be considered if oral mucosa and penile skin are not available, indicated, or desired.

Table 9.2: Outcome of case series of other autologous grafts

Study	Type of graft	N	Follow-up (months)	Stricture length (cm)	Urethral patency (%)
Bastian *et al*. 2012 [302]	Inguinal skin	34	70 (3-86)	8 (1.5-14)	91
Manoj *et al*. 2009 [550]	Postauricular skin	35	22 (3-48)	8.9 (3-15)	89
Meeks *et al*. 2010 [367]	Abdominal wall skin	21	28 (11-52)	11 (4-24)	81
Pfalzgraf *et al*. 2010 [351]	Split thickness skin graft	57/68	32	NR	84
Xu *et al*. 2009 [551]	Colonic mucosa	35	53.6 (26-94)	15.1 (10-20)	85.7

N = number of patients; NR = not reported.

Summary of evidence	LE
Patency rates of buccal mucosa and lingual mucosa are comparable.	1a
Different types of oral grafts have distinct types of oral morbidity and some of the oral complications might last in the long-term.	1a
Patency rates with penile skin grafts are 79-81.8% vs. 85.9-88.1% with buccal mucosa.	3
In LS related strictures, the use of genital skin graft is associated with poor patency rates (4%).	3

Recommendations	Strength rating
Use buccal or lingual mucosa if a graft is needed and these grafts are available.	Weak
Inform the patient about the potential complications of the different types of oral grafting (buccal vs. lingual vs. lower lip) when an oral graft is proposed.	Strong
Use penile skin if buccal/lingual mucosa is not available, suitable, or accepted by the patient for reconstruction.	Weak
Do not use genital skin graft in case of lichen sclerosus.	Strong

9.4 Tissue engineered grafts

*9.4.1 **Cell-free tissue engineered grafts***

These grafts are derived from cadaveric or animal sources (e.g., porcine small intestine submucosa [SIS], acellular bladder matrix, acellular dermal matrix), are completely cell-free and serve as a scaffold for host cell ingrowth [552]. The main advantage suggested for their use is the off-shelf availability [552].

A small RCT (n=30) comparing acellular bladder matrix with BMG reported a urethral patency rate of respectively 66.6% and 100%. The poorer results of acellular bladder matrix were the most apparent in cases of an unhealthy urethral bed [553]. Palminteri *et al*., reported a global urethral patency rate with SIS graft in 19/25 (76%) cases [554]. In this series SIS graft urethroplasty failed in all cases with a stricture length > 4 cm [554]. On the other hand, Xu *et al.,* reported adequate urethral patency in 26/28 patients (92.8%) after a median follow-up of 25 months. Of note, only one patient in this series underwent previous urethroplasty suggesting only minor spongiofibrosis in the remaining patients [555]. Other series have included only a limited number of patients with short follow-up. In these series, urethral patency rates vary between 20-100% [552].

Summary of evidence	LE
Patency rate of cell-free tissue engineered grafts decreases with large stricture length and unhealthy urethral bed.	1b

Recommendation	Strength rating
Do not use cell-free tissue engineered grafts in case of extensive spongiofibrosis, after failed previous urethroplasty or stricture length > 4 cm.	Weak

*9.4.2 **Autologous tissue engineered oral mucosa grafts***

These grafts contain a matrix seeded with autologous oral mucosa cells. Production requires a small oral mucosa biopsy (@ 0.5 cm^2) and the graft is further manufactured in the lab. The main advantage suggested is the reduction of oral donor site morbidity whereas the main disadvantages are costs and the strict time frame between manufacturing and implantation of the graft [552].

The clinical use of autologous tissue-engineered OMG was evaluated in a prospective, multicentre study including 99 patients [556]. Estimated twelve- and 24-months urethral patency rate was 67.3 and 58.2%, respectively. Oral adverse events were minimal. No comparative studies with acellular grafts or native OMGs are available nor are there any data about the cost-effectiveness [552].

Summary of evidence	LE
Safety, patency rate and cost-effectiveness of autologous tissue-engineered grafts is currently under research.	3

Recommendation	Strength rating
Do not use autologous tissue-engineered oral mucosa grafts outside the frame of a clinical trial.	Strong

9.5 Management of oral cavity after buccal mucosa harvesting

The post-operative morbidity of closure vs. non-closure of the buccal mucosa harvesting site has been evaluated by a number of prospective RCTs.

The results are summarised in Table 9.3. Based on these findings, no clear recommendation can be provided as to whether or not to close the harvesting site and the decision can be left to the treating physician.

Oral rinsing with chamomile [557] or chlorhexidine [545, 558] solution has been suggested in the first post-operative days without any evidence that this reduces pain or other oral complications.

Table 9.3: Effect of non-closure compared to closure on oral morbidity after buccal mucosa harvesting

Study	Early oral pain	Eating/ drinking problems	Altered taste	Altered salivation	Oral tightness	Perioral numbness	Oral bleeding	Slurred speech
Soave *et al*. [557]	=	=	=	=	=	=	=	=
Rourke *et al*. [559]	=	↓	NR	NR	↓	↓	=	NR
Muruganandam *et al*. [560]	↓	=	NR	=	=	=	=	NR
Wong *et al*. [558]	=	↑	NR	NR	=	=	=	NR
Lumen *et al*. [545]	↑	NR	NR	NR	NR	NR	NR	NR

↓ = less morbidity with non-closure; ↑ = more morbidity with non-closure; = = no significant difference; NR = not reported.

10. PERI-OPERATIVE CARE OF URETHRAL SURGERY

10.1 Urethral rest

After any form of urethral manipulation (urethral catheter, ISD, dilatation, DVIU), a period of urethral rest is necessary in order to allow tissue recovery and stricture “maturation” before considering urethroplasty. This improves the ability to identify the true extent of the fibrotic segments during subsequent surgery. If the patient develops incapacitating obstructive symptoms or urinary retention, a suprapubic catheter should be inserted. Terlecki *et al*., propose diagnostic evaluation after two months and urethroplasty after three months of urethral rest. These timings are based on the general principles of wound healing [561]. In their study, it has been shown that these periods allow for reliable stricture evaluation during urethrography which is, in turn, important to ensure selection of the most appropriate urethroplasty technique [561]. Utilising this strategy, similar outcomes were obtained compared to patients with stable previously unmanipulated strictures [561]. However, the optimal duration of urethral rest for all patients is not known and the degree of associated infection and inflammation should be taken into account as well, with longer periods of rest in those with greater degrees of infection and inflammation.

Summary of evidence	LE
After any form of urethral manipulation, a minimum period of three months urethral rest is necessary to allow for tissue healing before performing urethroplasty.	3

Recommendation	Strength rating
Do not perform urethroplasty within three months of any form of urethral manipulation.	Weak

10.2 Antibiotics

Post-operative wound infection and UTI are common post-operative complications and infection at the site of reconstruction may contribute to failure of urethroplasty. The vast majority of reconstructive urologists perform urine culture one to two weeks prior to surgery [562]. Urine culture is superior to urine-analysis which can be omitted in the pre-operative evaluation [562]. If infection or colonisation is present, a therapeutic course with antibiotics is recommended pre-operatively. In case of an indwelling catheter general principles would suggest at least an attempt to suppress the colonisation with pre-operative antibiotics [562]. These practices are in accordance with the strong recommendations of the EAU Guidelines on Urological Infections:

- "Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa."
- "Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions."

An intra-operative prophylactic regimen with antibiotics (according to local antibiotic resistance profiles) is effective in reducing the rate of post-operative surgical site and UTIs [562]. Although most urologists continue with post-operative antibiotics upon and even beyond catheter removal, there is no evidence that such a prolonged administration would reduce the infective complication rate [562]. The EAU Guidelines on Urological Infections do not routinely recommend the use of antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal. There is no evidence that this recommendation would not apply to catheter removal after urethral surgery.

Summary of evidence	LE
An intra-operative prophylactic regimen with antibiotics is effective in reducing the rate of postoperative surgical site and urinary tract infections.	4

Recommendation	Strength rating
Administer an intra-operative prophylactic regimen with antibiotics at time of urethral surgery.	Strong

10.3 Catheter management

After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period and it should be removed within 72 hours [563].

After one-stage urethroplasty and closure of the urethral plate after staged urethroplasty, urinary extravasation at the site of reconstruction must be avoided [564]. For this purpose, urinary diversion by either transurethral catheter or suprapubic catheter with urethral stent can be used. With respect to the type of catheter material, a prospective randomised (but underpowered) trial comparing silicone vs. hydrogel coated latex transurethral catheters showed no significant difference in the time to stricture recurrence nor in the overall recurrence rate [564]. The size of the urethral catheter utilised usually varies between 14 Fr and 20 Fr [565, 566]. Systematic use of anticholinergic drugs has not shown a significant reduction in the rate of involuntary pericatheter voiding whilst catheterised [567].

After urethroplasty an indwelling catheter is commonly left *in situ* for two to three weeks [566, 568]. After three weeks of urethral catheterisation, an extravasation rate of 2.2-11.5% at urethrography has been reported after different types of urethroplasty [568-571]. However, success with early catheter removal under three weeks has also been reported. A study after EPA for non-complicated anterior strictures demonstrated no significant difference in extravasation (6.8% vs. 4.5%) and recurrence rates (4.9% vs. 5.2%) between catheter removal at one or two weeks respectively [572]. Poelaert *et al*., reported an extravasation rate of 3.5% vs. 8.3%, when the catheter was removed ≤ 10 days or > 10 days respectively after all types of urethroplasty (n=219) (p=0.158) [565]. Importantly, patients who had a duration of catheterisation of > 10 days had longer and more complex strictures [565].

Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation [568, 570]. Importantly, some authors have identified urinary extravasation as a predictive factor for stricture recurrence [565, 573]. Other series, however, could not confirm the prognostic significance of urinary extravasation but they included any form of extravasation (including minor leaks) [570, 571]. Grossgold *et al*., found that high-grade leaks (defined as length ≥ 1.03 cm and width ≥ 0.32 cm) were significantly associated with higher restricture rates. This study also found length of extravasation > 1.03 cm alone to be an independent predictor of restricture [573]. In cases of persistent and significant urinary extravasation, the catheter should be maintained or reinserted and the examination repeated after one week [568]. However, low-grade ("wisp-like") extravasation does not appear to affect long-term restricture rate and the catheter can be removed in these cases without subsequent urethrogram [570, 573]. In case of any doubt about the significance of extravasation, it is safe to keep the catheter in for an additional week and ReDo the assessment.

The assessment of urinary extravasation is achieved by either pericatheter retrograde urethrography (pcRUG), classic RUG or VCUG [568]. Voiding cystourethrography (after catheter removal) is the most physiologic examination as it shows the urethra under normal intra-urethral pressures and using this test residual urethral narrowing is most accurately identified. This has been found to be a strong prognostic factor for failure in a series evaluating bulbar FGU [571]. In contrast, pcRUG is associated with supraphysiological intra-urethral pressures and a potentially higher chance of false positive results [568, 573]. Although there is no evidence that one imaging modality is superior to the other, pcRUG should be performed if there is a high-risk of leakage as it avoids the need for catheter reinsertion through a recently reconstructed urethra in case of a positive exam. High risk of leakage depends on the complexity of urethroplasty (e.g., stricture length > 10 cm, panurethral repair) [570, 573]. External clinical signs of impaired wound healing (e.g., abscess formation, wound dehiscence) are also associated with a high risk (71.4%) of leakage [565]. In cases of attempted VCUG where the patient is not able to void during fluoroscopy after catheter removal, RUG should be performed [573].

Although limited evidence for urethroplasty care in trans men exists, one study advised a three-week period of transurethral catheterisation with pcRUG upon catheter removal [514].

After perineostomy or the 1st stage of staged urethroplasty, the catheter can be removed without need for urethrography after three to five days [349, 570].

Summary of evidence	LE
Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation with urethrography to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation.	2b
After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period.	3
Early catheter removal may be appropriate for a subset of patients with short, uncomplicated, strictures.	3

Recommendations	Strength rating
Perform a form of validated urethrography after urethroplasty to assess for urinary extravasation prior to catheter removal.	Strong
Remove the catheter within 72 hours after uncomplicated direct vision internal urethrotomy or urethral dilatation.	Weak
Consider 1st urethrography seven to ten days after uncomplicated urethroplasty to assess whether catheter removal is possible, especially in patients with bother from their urethral catheter.	Weak

11. FOLLOW-UP

11.1 Rationale for follow-up after urethral surgery

The rationale for following-up patients after urethral stricture surgery is to detect and manage any complication or recurrence. As with any surgical procedure, following urethroplasty some patients will present with complications at short to medium follow-up: approximately 38% with bulbar urethroplasties [322] and up to 54% for all anterior urethroplasties [574]. Most of these complications (92%) would be classified as Clavien

grade 1 or 2 [322]. Even though urethroplasty techniques provide the highest chances for successful treatment of urethral strictures, some patients will experience recurrence [326]. For further details on particular outcomes in each urethral segment, please review the individual chapters of this Guideline.

Summary of evidence	LE
After urethroplasty surgery, recurrent strictures appear with different frequency depending on stricture features and urethroplasty techniques.	3

Recommendation	Strength rating
Offer follow-up to all patients after urethroplasty surgery.	Strong

11.2 Definition of success after urethroplasty surgery

The “traditional academic” definition of post-operative success after urethroplasty has been considered as “The lack of any post-operative intervention for restricture” [575]. This definition, despite being widely used [307, 322] is problematic as it ignores asymptomatic or even symptomatic recurrences in patients not willing to undergo further surgeries [575]. There is some variation as to what is considered intervention with some groups accepting endoscopic treatments as success, while considering failure only as the requirement for a ReDo urethroplasty [308].

A more objective definition of success is the “anatomic success”, defined as “Normal urethral lumen during RUG or cystoscopy, regardless of patient symptoms”. Using this definition, stricture recurrence or anatomical failure is considered by some groups as urethral narrowing found to be endoscopically impassable – without force – with a 16 Fr flexible endoscope [143, 576]. This definition is certainly stricter, with up to 35% of cystoscopic recurrences after bulbar urethroplasty remaining asymptomatic, and thus would have been considered as successful if a “lack of further intervention” definition was used [143]. Other groups consider cystoscopic recurrence as any stricture that is visible on post-operative cystoscopy, even the so-called “large calibre re-strictures” (> 17 Fr) [141]. Not all anatomic recurrent strictures would need further treatment [575]. It was suggested to intervene when the anatomic recurrence is associated with recurrence of symptoms, stricture-related high post-void residuals or a stricture calibre of < 14 Fr – even if these are asymptomatic [575].

Over the last ten years, the evaluation of urethral surgery outcomes has shifted towards a “patient-reported definition of success”. The aim of any urethral intervention is to allow patients to return to a normal state of voiding while maintaining QoL [577] or to minimise symptoms, reduce disability, and improve HRQoL by restoring normal urinary function [578]. Even if the surgeon reconstructed a wide and patent urethra, if patients experience pain, sexual dysfunction or perceive their urinary function as not improved, they will not rate their outcome as successful [575]. On a multivariate analysis including both patient-reported and clinical parameters, urine flowmetry parameters failed to demonstrate significant contribution to satisfaction [579]. Kessler *et al*., reported that only 78.3% of patients with clinical success described themselves as (very) satisfied. More dissatisfaction significantly appeared with penile curvature, penile shortening, worsening of erectile function and impairment of sexual life [580]. Conversely, 80% of patients defined as clinical failures considered themselves as (very) satisfied with their outcomes [580]. Regardless of anatomic success after urethroplasty, post-operative pain, sexual dysfunction and persistent LUTS were independent predictors of patient dissatisfaction [579]. Improvement in voiding function (i.e., statistical improvement on IPSS) alone does not predict patient satisfaction after urethroplasty [581]. On a multivariate analysis including both patient-reported and clinical parameters, after adjusting for disease recurrence and age, persistence in voiding symptoms (weak stream), genitourinary pain, and post-operative sexual function alterations were the greatest independent drivers of post-operative dissatisfaction [579]. In addition, penile shortening (OR: 2.26; 95% CI: 1.39-3.69) and chordee (OR: 2.26; 95% CI: 1.44-4.19) were independent predictors of patient dissatisfaction after urethroplasty [581] (Table 11.1).

Table 11.1: Predictors of patient dissatisfaction after urethral surgery

Predictor/Symptoms	Measure of effect	Authors
Weak/very weak urinary stream	< 0.001	Kessler TM *et al*. J Urol 2002 [580]
Penile curvature	0.001	
Penile shortening	0.001	
Worsening of erectile function	0.001	
Impairment of sexual life	< 0.001	
Sexual activity alteration	OR: 4.36 (1.54 – 12.37)*	Bertrand LA *et al*. J Urol 2016 [579]
Erection confidence (SHIM)	OR: 1.53 (1.12 – 2.07)*	
Inability to ejaculate (MSHQ)	OR: 1.52 (1.15 – 2.01)*	
Urethral pain	OR: 1.71 (1.05 - 2.77)*	
Bladder pain	OR: 2.74 (1.12 – 6.69)*	
Urinary strain (CLSS)	OR: 3.23 (1.74 – 6.01)*	
Hesitancy (IPSS)	OR: 2.01 (1.29 – 3.13)*	
Voiding quality of life (IPSS)	OR: 1.96 (1.42 – 2.72)*	
Penile shortening	OR: 2.26 (1.39-3.69)**	Maciejewski CC *et al*. Urology 2017 [581]
Chordee	OR: 2.26 (1.44 – 4.19)**	

** p < 0.05; ** p < 0.001.*
SHIM = Sexual Heath Inventory for Men; MSHQ = Male Sexual Health Questionnaire;
CLSS = Core Lower Urinary Tract Symptom Score; IPSS = International Prostate Symptoms Score.

Due to this evident discrepancy between surgeon's assessment and patient assessment, PROMs have been developed for the follow-up after urethroplasty [158, 578].

A complete approach for urethral surgery outcomes would combine both anatomic, endoscopic, and patient-reported success [324, 575]. The Panel suggest using a functional definition of success in clinical practice, namely "lack of symptoms and/or need for further interventions".

Collecting standardised documentation of the patient's subjective assessment of their symptoms and objective anatomic outcomes would be limited for academic purposes, in order to allow comparison of surgical outcomes among reconstructive urologic surgeons and centres. Those objective and subjective outcomes measures should therefore be assessed and reported (simultaneously but separately) when evaluating urethroplasty results [575].

11.3 Follow-up tools after urethral surgery

*11.3.1 **Diagnostic tools for follow-up after urethral surgery***

11.3.1.1 Calibration during follow-up after urethral surgery

The difference between calibration and urethral dilatation is usually subjective as soft strictures may be dilated during calibration [582]; therefore, urethral calibration should be used with caution for follow-up after urethroplasty. Dedicated calibration bougies should be used and not dilatators.

11.3.1.2 Urethrocystoscopy during follow-up after urethral surgery

Urethrocystoscopy has been considered the most useful tool to confirm the presence or absence of a recurrent stricture [141, 583], as up to 35% of patients with re-strictures remain asymptomatic [143]. Also, the cystoscope could be a measure to calibrate the strictured lumen, bearing in mind the most commonly used endoscopes: 15.7 Fr (5 mm diameter) or 17.3 Fr (5.5 mm diameter) [583]. Urethrocystoscopy allows differentiation of recurrences as diaphragm/cross-bridging – responding to simple intervention, or significant urethral restrictures – requiring repeated interventions or ReDo surgeries [584]. Endoscopic assessment at three months after anterior urethroplasty can predict the risk for further re-intervention at one year. Compared to normal endoscopy, large calibre (> 17 Fr) restrictures have a HR of 3.1 (1.35-7.29) for repeat intervention while small calibre (< 17 Fr) restrictures have a 23.7 HR (12.44-45.15) adjusted for age, stricture length, location, and aetiology [141]. The main problem with using urethrocystoscopy for routine follow-up is the low compliance of patients as only 54% of patients underwent endoscopy at one year after urethroplasty, even when it was a part of a study protocol [143].

11.3.1.3 Retrograde urethrogram and voiding cystourethrogram during follow-up after urethral surgery

Retrograde urethrogram combined with VCUG are commonly used to confirm suspected recurrence [585, 586] or as part of a routine protocol to assess post-operative urethral patency [587, 588].

11.3.1.4 Urethral ultrasound – Sonourethrography during follow-up after urethral surgery

The use of SUG as a follow-up tool is not very common. It would be a reliable tool for diagnostic recurrent strictures [585].

11.3.2 ***Screening tools for follow-up after urethral surgery***

These tools are used to assess whether there is suspicion of stricture recurrence and need for subsequent diagnostic evaluation (see section 5. Diagnostic evaluation).

11.3.2.1 Flow-rate analysis during follow-up after urethral surgery

Evaluating the Q_{max} is the commonest follow-up tool. Different cut-off points from Q_{max} 15 ml/s or 12 ml/s were suggested to consider the intervention as a failure or to trigger a confirmatory test for recurrence [587]. There is no clear threshold, and 19% of patients with Q_{max} < 14 ml/s would still have a patent urethra, allowing passage of 15 Fr cystoscope [144].

Flow rates may be affected by operator error, BPO/LUTS, bladder dysfunction, and variations in bladder capacity. Further limitations of uroflowmetry include the need for a minimum voided volume of 125-150 ml to reach a voided flow rate that reliably predicts an abnormality [582]. Even in controlled settings, the percentage of patients with adequate pre- and post-operative uroflowmetry analysis is only 31% [588]. Comparing both pre- and post-operative Q_{max} levels was suggested, and a difference in Q_{max} of 10 ml/s or less is found to be a reliable screen tool for recurrence (sensitivity 92%, specificity 78%). This measure also has strong reproducibility (R=0.52) [588]. Unfortunately, this improvement after urethroplasty is significantly different between age groups, with less than 10 ml/s average change in those over 65 years old, probably affected by BPO and/or bladder dysfunction [589]. Another parameter to consider is the shape of the voiding curve, recording it as flat (obstructed) or bell-shaped [590]. An obstructive voiding curve demonstrated 93% sensitivity to predict recurrent strictures, while a combination of urinary symptoms and obstructive voiding curve achieved 99% sensitivity and 99% NPV [590].

11.3.2.2 Post-void residual ultrasound measure during follow-up after urethral surgery

Post-void residual US measure is significantly increased in patients with recurrent strictures compared with those without recurrences [585]. Unfortunately, PVR measurement is affected by abdominal ascites, bladder diverticula and/or poor bladder function [582], with some studies reporting inconsistent correlation with obstruction in the presence of BPO. Also, US measures of PVR are user dependent, showing high interobserver variability. Combined with other tests – uroflowmetry, IPSS, and SUG – PVR achieves adequate predictive values [585], but currently there is no literature to support its solo use, to assess urethral stricture recurrence [591].

11.3.2.3 Symptom questionnaires during follow-up after urethral surgery

The IPSS questionnaire, despite being designed for BPO, showed significant improvement after successful urethroplasty and inverse significant correlation with Q_{max} [581, 582]. The mean improvement of IPSS is around -11 points (range -19 to -5) [589].

Table 11.2: Post-urethroplasty changes in IPSS values

Author	N	Mean pre-operative value	Mean post-operative value	Change	Significancy
Morey AF *et al*. 1998 [592]	50	26.9	4.4	NR	p < 0.0001
DeLong J *et al*. 2013 [589]	110	NR	NR	-11 (IQR -19 - -5)	p < 0.001
Maciejewski CC *et al*. 2017 [581]	94	18.7 (+/- 9)	5.8 (+/- 5)	NR	p < 0.0001

N = number of patients; NR = not reported; IPSS = International Prostate Symptoms Score; IQR = interquartile range.

Combination of IPSS and Q_{max} analysis was suggested to diagnose recurrences. Using an IPSS cut-off point of 10 points associated with Q_{max} > 15 ml/s would prevent further invasive studies in 34% of patients, while only 4.3% of strictures < 14 Fr would have been missed. Using an IPSS cut-off point of 15 points associated with Q_{max} > 15 ml/s would prevent further invasive studies in 37% of cases, while 6% of strictures < 14 Fr would have been missed [593].

The Visual Prostate Symptom Score (VPSS) was also used to diagnose recurrent urethral strictures, offering a significantly shorter time to completion compared with IPSS, especially in cases of illiteracy or limited education. Visual Prostate Symptom Score showed a good correlation with IPSS, Q_{max} and urethral diameter. A combination of VPSS > 8 with Q_{max} < 15 ml/s had a NPV of 89% and a PPV of 87% for recurrent urethral strictures [594].

Post-micturition dribble, assessed by the specific question of the USS-PROM questionnaire, was present in 73% of patients pre-operatively and 40% after anterior urethroplasty, while only 6.3% was *de novo*. Incidence was not predicted by stricture location nor urethroplasty type [148].

*11.3.3 **Quality of life assessment, including disease specific questionnaires during follow-up after urethral surgery***

Urethral stricture affects QoL evaluated by EQ-5D-3L questionnaire. Pre-operative anxiety and depression was found in 29% of patients. *De novo* AD after urethroplasty is uncommon (10%) and has two predictors: decreased sexual function and poor reported image of overall health [595]. A more recommended approach is the assessment of the condition-related QoL [596]. The USS-PROM proved useful to assess outcomes in anterior urethroplasty patients [578]. Its use also received criticism, as some of the individual generic QoL questions do not improve after successful urethroplasty, as they are not condition-specific [597]. Currently, there is another version of PROM, being developed and validated by a North American collaborative group, including questions related to the sexual consequences of urethral stricture disease [159]. PROM questionnaires should be implemented in each visit to check for functional success, as they are able to show improvement over time.

The Core Lower Urinary Tract Symptom Score (CLSS) questionnaire was used to assess pre- and post-urethroplasty pain in the bladder, penis/urethra, and perineum/scrotum. Most of the parameters improved after urethroplasty, but up to 29% of patients reported worsening of perineal pain after surgery [598].

Sexual function should be evaluated by validated tools if not assessed in a PROM. The international index on erectile function (IIEF), SHIM, O´Leary Brief Male Sexual Function Inventory (BMFSI), SLQQ (Sexual Life Quality Questionnaire), Male Sexual Health Questionnaire (MSHQ) have all been used after urethroplasties for evaluation of erectile and ejaculatory functions. Other non-validated tools were suggested such as the Post-Urethroplasty Sexual Questionnaire (PUSQ) [599] or specific questionnaires for genital appearance (length, curvature) or sensitivity [600].

Summary of evidence	**LE**
Retrograde urethrography and urethrocystoscopy are able to identify anatomical success after a urethroplasty.	2a
A significant gap was demonstrated between objective and subjective outcomes after urethroplasties. PROM questionnaires are specific tools to assess subjective outcomes and patient satisfaction after urethroplasty surgeries.	2a
Validated questionnaires proved useful to assess the consequences of urethral surgery on sexual function.	2a

Recommendations	**Strength rating**
Use cystoscopy or retrograde urethrography to assess anatomic success after urethroplasty surgery.	Weak
Use patient reported outcome measure questionnaires to assess subjective outcomes and patient satisfaction.	Strong
Use validated questionnaires to evaluate sexual function after urethral stricture surgeries.	Strong

11.4 Ideal follow-up interval after urethral surgery

The optimal follow-up strategy must allow for an objective determination of anatomic and functional outcomes to assess surgical success whilst avoiding excessive invasive testing that leads to unnecessary cost, discomfort, anxiety, and risk [575].

After anterior urethroplasty, 21% of recurrences are clinically evident, and cystoscopically confirmed, after three months [601] and 96% after one year [584]. Early recurrences are more frequent in patients with LS and older age, in longer strictures and when skin grafts were used [601].

11.5 Length of follow-up after urethral surgery

The median time of recurrence after bulbar urethroplasty is approximately ten months [328]. In case series, between 55.4% [601] and 96% [584, 587] of all recurrences are detected during the first year of follow-up after urethral surgery. Twenty-three percent of bulbar stricture recurrences are detected during the second year of follow-up, and the percentage of recurrences decreases after the second year [326].

On the other hand, long-term follow-up studies highlighted the role of length of follow-up as a predictor for stricture recurrence after bulbar urethroplasty [326, 603]. Late recurrences – later than five years after urethroplasty – could be observed in up to 15% of cases [144, 326]. This should be considered mainly after augmentation urethroplasties, especially in case skin grafts were used [586]. Certainly, patients should be instructed to seek urological evaluation if they experience late recurrent symptoms [603].

11.6 Risk-stratified proposals during follow-up after urethral surgery

Cost of follow-up after urethroplasty is higher in the first year after the procedure [602]. In a literature review it ranged between 205 to 1,784 US Dollars, with higher costs associated to posterior urethral repairs [602]. As the risk of recurrence and side effects are related to the type of stricture and urethroplasty, a different follow-up schedule was proposed and shown to be cost-effective in the USA, potentially saving up to 85% of costs after five years [576]:

- Urethroplasties with a low risk of recurrence (EPA urethroplasty without history of radiotherapy, hypospadias, or LS features) could be safely followed up based on monitoring of symptoms, using self-administered IPSS questionnaire, every three months for one year, and annually thereafter.
- Urethroplasties with standard risk of recurrence (urethroplasty using grafts, flaps, and/or post-irradiation, hypospadias and/or LS patients) could combine IPSS questionnaire + flowmetry every three months for one year, and annually thereafter. Additionally, RUG at three and twelve months should be performed.

In this protocol, urethrocystoscopy is only performed if required [576]. Another suggested follow-up protocol includes urethrocystoscopy or RUG/VCUG at three months post-operatively, in order to rule out early failures, especially in case of graft use. If there is evidence of good anatomical outcome in these tests, flowmetry and questionnaire results at three months should be considered as the new baseline. Thereafter, follow-up could be safely and routinely performed with non-invasive tests (flowmetry – evaluating Q_{max} and the shape of curve – and questionnaires). Any deterioration should be further investigated with a urethrocystoscopy [591].

A recently suggested protocol also included assessment of LUTS, sexual function (erectile and ejaculatory), and LUT pain, that need to be compared with pre-operative findings which should include a PROM questionnaire [575]. Cystoscopy and flowmetry should be performed between three to six months postoperatively, and flowmetry findings should be considered as the new baseline for longitudinal follow-up. Future significant decline (25-30%) in Q_{max} or Q_{max} - (average flow rate) should trigger new cystoscopy to rule out anatomic recurrence, even in patients who are symptom-free [575]. A routine cystoscopy at twelve to fifteen months should be performed at the surgeon's discretion, based on risk assessment of three aspects: higher-risk patients, evidence of partial urethral narrowing at three-month assessment, low-volume surgeons [575].

Summary of evidence	**LE**
The higher percentage of recurrences presents during the first twelve months, after urethroplasty surgery.	2a
Risk-adjusted follow-up protocols are cost-effective and safe for the patients.	3

Recommendations	**Strength rating**
Offer a routine follow-up of at least one year after urethroplasty.	Strong
Adopt a risk-adjusted follow-up protocol.	Weak

11.7 Follow-up protocol proposal after urethroplasty

*11.7.1 **Surgeries with low risk of recurrence***

- Anastomotic urethroplasties in the bulbar/(bulbo)membranous segment with no history of radiotherapy, hypospadias, or balanitis xerotica obliterans (BXO)/LS features.

Table 11.3: Follow-up protocol for urethroplasty with low risk of recurrence

Surgery	3 months	12 months	24 months*
Uroflowmetry	+	+	+
PROM (incl. sexual function)	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+**	On indication	On indication

**Follow-up could be discontinued after two years, advising the patient to seek urological evaluation if symptoms worsen. Academic centres could increase the length of follow-up for research purposes.*
***The Panel suggests performing an anatomic assessment at three months.*

*11.7.2 **Surgical management options with standard risk of recurrence***

- Anastomotic urethroplasties in the bulbar segment with prior history of radiotherapy, hypospadias, or BXO/LS features;
- Penile urethroplasties;
- Non-traumatic posterior urethroplasties;
- Graft or/and flap – substitution – urethroplasties.

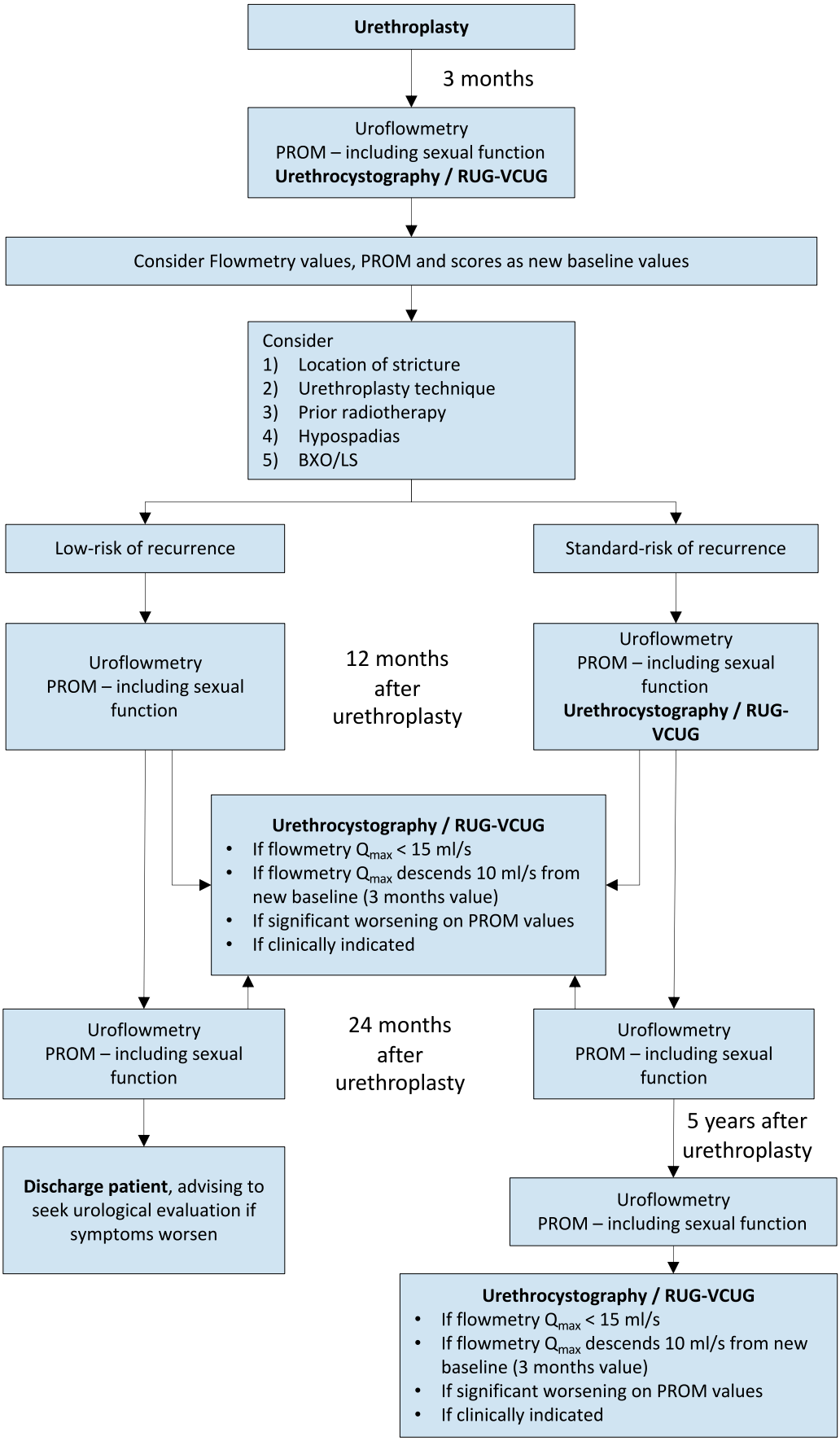
Table 11.4: Follow-up protocol for urethroplasty with standard risk of recurrence

Surgery	3 months	12 months	24 months	5 years *
Uroflowmetry	+	+	+	+
PROM (incl. sexual function)	+	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+	+	+	On indication

** Follow-up could be discontinued after five years, advising the patient to seek urological evaluation if symptoms worsen. A longer follow-up period should be considered after penile and substitution urethroplasties. Academic centres could increase the length of follow-up for research purposes.*

Please see Figure 11.1 for further guidance.

Figure 11.1: Follow-up after urethroplasty


Urethroplasty
3 months
Uroflowmetry
PROM – including sexual function
Urethrocystography / RUG-VCUG
Consider Flowmetry values, PROM and scores as new baseline values
Consider
1) Location of stricture
2) Urethroplasty technique
3) Prior radiotherapy
4) Hypospadias
5) BXO/LS
Low-risk of recurrence
Standard-risk of recurrence
Uroflowmetry
PROM – including sexual function
12 months after urethroplasty
Uroflowmetry
PROM – including sexual function
Urethrocystography / RUG-VCUG
Urethrocystography / RUG-VCUG
If flowmetry Qmax < 15 ml/s
If flowmetry Qmax descends 10 ml/s from new baseline (3 months value)
If significant worsening on PROM values
If clinically indicated
Uroflowmetry
PROM – including sexual function
24 months after urethroplasty
Uroflowmetry
PROM – including sexual function
5 years after urethroplasty
Discharge patient, advising to seek urological evaluation if symptoms worsen
Uroflowmetry
PROM – including sexual function
Urethrocystography / RUG-VCUG
If flowmetry Qmax < 15 ml/s
If flowmetry Qmax descends 10 ml/s from new baseline (3 months value)
If significant worsening on PROM values
If clinically indicated

BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient reported outcome measure; Q_{max} = maximum flow rate; RUG = retrograde urethrography; VCUG = voiding cystourethrography.

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13. CONFLICT OF INTEREST

All members of the Urethral Strictures Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

14. CITATION INFORMATION

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urolithiasis Guidelines Panel has prepared these guidelines to help urologists assess evidence-based management of stones/calculi in the urinary tract and incorporate recommendations into clinical practice. This document covers most aspects of the disease, which is still a cause of significant morbidity despite technological and scientific advances. The Panel is aware of the geographical variations in healthcare provision. Originally available as a separate document, information on the management of bladder stones is now also included in these guidelines.

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urolithiasis Guidelines Panel consists of an international group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU, website Uroweb: http://uroweb.org/guideline/urolithiasis/.

1.3 Available publications

A quick reference document (Pocket guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions, which may require consultation together with the full text versions. Several scientific publications are also available [1-3]. All documents can be accessed through the EAU website: http://uroweb.org/guideline/urolithiasis/.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU Urolithiasis Guidelines were first published in 2000. This 2022 document presents a limited update of the 2021 version.

*1.4.2 **Summary of changes***

The literature for the entire document has been checked and, wherever relevant, updated (see Methods section 2.1). References and supporting text have also been refreshed.

For 2022, several new sections have been added to these guidelines. These include chapter 3.5. Radiation exposure and protection during endourology and chapter 5. Follow-up of urinary stones. Throughout the text passages on best clinical practice for the use of different interventions have been added to the relevant sections. In addition, chapter 3.4.3 Medical expulsive therapy has been thoroughly revised and the Bladder Stones guidelines, previously a separate document, have been integrated into this text. Four new algorithms have also been added:

- Figure 4.2: Diagnostic algorithm for calcium oxalate stones
- Figure 4.6: Diagnostic algorithm for uric acid stones
- Figure 5.1: Follow-up duration of urinary stone patients after treatments
- Figure 5.2: Consensus on follow-up frequency and imaging modality to use after treatment

2. METHODS

2.1 Data identification

For the 2022 Urolithiasis Guidelines, new and relevant evidence has been identified, collated, and appraised through a structured assessment of the literature.

A broad and comprehensive scoping exercise covering all areas of the guideline was performed. The search was limited to studies representing high levels of evidence only (i.e., systematic reviews with meta-analysis (MA), randomised controlled trials (RCTs), and prospective non-randomised comparative studies) published in the English language. The search was restricted to articles published between 1st May 2020 and 12th May 2021. A total of 737 unique records were identified and screened for relevance.

For the 2022 Bladder Stones section, new and relevant evidence was identified, collated, and

appraised through a structured assessment of the literature. The search was limited to studies representing high levels of evidence only published in the English language. The search was restricted to articles published between April 2020 and April 2021. A total of 235 unique records were identified and screened for relevance.

In addition to this, several ancillary searches limited to studies representing high levels of evidence only and published in the English language were also carried out to underpin the new chapter 3.5. radiation exposure and protection during endourology, and to formulate best clinical practice statements. The five-year search, from 2016 to May 2021, on radiation exposure and urolithiasis returned a total of 117 unique records which were identified and screened for relevance. The remainder of the searches on specific interventions that could be used to formulate best clinical practice statements returned a total of 1,080 records which were identified and screened for relevance. These include a four-year search (2018-2021) on URS thulium fiber laser; five-year searches (2017-2021) on URS internal temperature, URS suction with fragmentation, URS intrarenal pressure, fluoroless URS, PNL suction, and PNL fluoroless; a six-year search (2016-2021) on single vs. reusable URS, and ten-year searches (2011-2021) on SWL, URS fibreoptic vs. digital, optimal laser, URS time limit operation, PNL anaesthesia, PNL thermal and PNL renal puncture.

Databases covered by the searches included Medline, EMBASE, Ovid and the Cochrane Libraries. The search strategies are published online: http://uroweb.org/guideline/urolithiasis/?type=appendices-publications.

A total of 59 new references have been added to the 2022 Urolithiasis Guidelines publication. The chapters on the treatment of bladder stones in adults and children are based on a systematic review [4].

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [5, 6]. Each strength-rating form addresses a number of key elements, namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [7];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words ‘strong’ or ‘weak’ [8]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/.

A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The 2015 Urolithiasis Guidelines were subjected to peer-review prior to publication. Chapter 6, detailing the treatment and follow-up of bladder stones was peer reviewed in 2019.

2.3 Future goals

For the 2023 text update the Urolithiasis Guidelines Panel aim to provide further guidance on the following topics:

- Further evaluate the highest evidence for best clinical practice in endourology.
- Perform a systematic review on patient and personnel radiation protection during endourology.
- Questioning the accuracy of stone size as the surrogate index for deciding upon the treatment of urinary stones.

3. GUIDELINES

3.1 Prevalence, aetiology, risk of recurrence

3.1.1 Introduction

Stone incidence depends on geographical, climatic, ethnic, dietary, and genetic factors. The recurrence risk is basically determined by the disease or disorder causing the stone formation. Accordingly, the prevalence rates for urinary stones vary from 1% to 20% [9]. In countries with a high standard of life such as Sweden, Canada or the USA, renal stone prevalence is notably high (> 10%). For some areas, an increase of more than 37% over the last 20 years has been reported [10-12]. There is emerging evidence linking nephrolithiasis to the risk of chronic kidney disease (CKD) [13].

Stones can be stratified into those caused by: infections, non-infectious causes, genetic defects [14]; or adverse drug effects (drug stones) (Table 3.1). See also section 3.2.

Table 3.1: Stones classified by aetiology

Non-infection stones		
• Calcium oxalate	• Calcium phosphate	• Uric acid
Infection stones		
• Magnesium ammonium phosphate	• Highly-carbonated apatite	• Ammonium urate
Genetic causes		
• Cystine	• Xanthine	• 2,8-Dihydroxyadenine
Drug stones		

3.1.2 Stone composition

Stone composition is the basis for further diagnostic and management decisions. Stones are often formed from a mixture of substances. Table 3.2 lists the most clinically relevant substances and their mineral components.

Table 3.2: Stone composition

Chemical name	**Mineral name** [15]	**Chemical formula**
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4.H_2O$
Calcium oxalate dihydrate	Weddelite	$CaC_2O_4.2H_2O$
Basic calcium phosphate	Apatite	$Ca_{10}(PO_4)_6.(OH)_2$
Calcium hydroxyl phosphate	Carbonate apatite	$Ca_5(PO_4)_3(OH)$
b-tricalcium phosphate	Whitlockite	$Ca_3(PO_4)_2$
Carbonate apatite phosphate	Dahllite	$Ca_5(PO_4)_3OH$
Calcium hydrogen phosphate dihydrate	Brushite	$CaHPO_4.2H_2O$
Calcium carbonate	Aragonite	$CaCO_3$
Octacalcium phosphate	-	$Ca_8H_2(PO_4)_6.5H_2O$
Uric acid	Uricite	$C_5H_4N_4O_3$
Uric acid dihydrate	Uricite	$C_5H_4O_3.2H_20$
Ammonium urate	-	$NH_4C_5H_3N_4O_3$
Sodium acid urate monohydrate	-	$NaC_5H_3N_4O_3.H_2O$
Magnesium ammonium phosphate hexahydrate	Struvite	$MgNH_4PO_4.6H_2O$
Magnesium acid phosphate trihydrate	Newberyite	-
Magnesium ammonium phosphate monohydrate	Dittmarite	-
Cystine	-	-
Xanthine	-	-
2,8-Dihydroxyadenine	-	-
Proteins	-	-
Cholesterol	-	-
Calcite	-	-
Potassium urate	-	-
Trimagnesium phosphate	-	-
Melamine	-	-
Matrix	-	-
Drug stones	Active compounds crystallising in urine	-
Foreign body calculi	-	-

3.1.3 Risk groups for stone formation

The risk status of stone formers is of particular interest because it defines the probability of recurrence or regrowth, the risk of CKD and mineral and bone disorder, and is imperative for pharmacological treatment. About 50% of recurrent stone formers have just one lifetime recurrence [11, 16]. A recent review of first-time stone formers calculated a recurrence rate of 26% in five years' time [17]. Highly recurrent disease is observed in slightly more than 10% of patients. Stone type and disease severity determine low- or high-risk stone formers (Table 3.3) [18, 19].

Table 3.3: High-risk stone formers [18-34]

General factors
Early onset of urolithiasis (especially children and teenagers)
Familial stone formation
Recurrent stone formers
Short time since last stone episode
Brushite-containing stones ($CaHPO_4.2H_2O$)
Uric acid and urate-containing stones
Infection stones
Solitary kidney (the kidney itself does not particularly increase the risk of stone formation, but prevention of stone recurrence is of more importance)
Diseases associated with stone formation
Hyperparathyroidism
Metabolic syndrome
Nephrocalcinosis
Polycystic kidney disease (PKD)
Gastrointestinal diseases (i.e., jejuno-ileal bypass, intestinal resection, Crohn's disease, malabsorptive conditions, enteric hyperoxaluria after urinary diversion, exocrine pancreatic insufficiency) and bariatric surgery
Increased levels of vitamin D
Sarcoidosis
Spinal cord injury, neurogenic bladder
Genetically determined stone formation
Cystinuria (type A, B and AB)
Primary hyperoxaluria (PH)
Renal tubular acidosis (RTA) type I
2,8-Dihydroxyadeninuria
Xanthinuria
Lesch-Nyhan syndrome
Cystic fibrosis
Drug-induced stone formation (see Table 4.11)
Anatomical abnormalities associated with stone formation
Medullary sponge kidney (tubular ectasia)
Ureteropelvic junction (UPJ) obstruction
Calyceal diverticulum, calyceal cyst
Ureteral stricture
Vesico-uretero-renal reflux
Horseshoe kidney
Ureterocele
Environmental and professional factors
High ambient temperatures
Chronic lead and cadmium exposure

A comprehensive evaluation of stone risk in patients should also include the risk of developing CKD, end-stage kidney disease (ESKD), and metabolic stone disease (Tables 3.4, 3.5 and 3.6). Urolithiasis can compromise renal function because of the renal stone (obstruction, infection), renal tissue damage due to the primary condition causing stone formation (some genetic diseases, nephrocalcinosis, enteric hyperoxaluria, etc.), or urological treatments for the condition [35]. Certain risk factors have been shown to be associated with such a risk in stone formers, as shown below.

Table 3.4 Risk factors for CKD and ESKD in stone formers

Risk factors for CKD/ESKD in stone formers
Female gender
Overweight
Frequent UTI
Struvite stones
Acquired single kidney
Neurogenic bladder
Previous obstructive nephropathy
Ileal conduit

Furthermore, some specific kinds of urolithiasis also carry a particular risk of developing CKD/ESKD as shown below.

Table 3.5 Risk factors for CKD and renal stones

Risk of chronic kidney disease and renal stones
• Possible risk of CKD
■ Xanthine stones
■ Indinavir stones
■ Distal renal tubular acidosis (incomplete)
■ Primary hyperparathyroidism
■ Eating disorders and laxative abuse
■ Medullary sponge kidney
• Moderate risk of CKD
■ Brushite stones
■ 2,8-Dihydroxyadenine stones
■ Sarcoidosis
■ Pyelo-ureteral or ureteral strictures
• High risk of CKD
■ Cystine stones
■ Struvite stones
■ Stones in a single kidney
■ Distal renal tubular acidosis (complete)
■ Secondary hyperoxaluria (bariatric surgery, inflammatory bowel disease, bowel resection and malabsorptive syndromes)
■ Other forms of nephrocalcinosis (often associated with genetic conditions with hypercalciuria)
■ Anatomical abnormalities of the kidney and urinary tract (for example, horseshoe kidney, ureterocele and vesicoureteral reflux)
■ Neurological bladder
• Very high risk of CKD
■ Primary hyperoxaluria
■ Autosomal dominant polycystic kidney

Table 3.6 Risk factors for metabolic bone disease and calcium renal stones

Risk of metabolic bone disease and calcium renal stones
• Distal renal tubular acidosis (complete or incomplete)
• Medullary sponge kidney
• Primary hyperparathyroidism
• Malabsorptive syndromes
• Fasting hypercalciuria
• Genetic disorders

3.2 Classification of stones

Urinary stones can be classified according to size, location, X-ray characteristics, aetiology of formation, composition, and risk of recurrence [11, 36, 37].

*3.2.1 **Stone size***

Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in largest diameter.

*3.2.2 **Stone location***

Stones can be classified according to anatomical position: upper, middle, or lower calyx; renal pelvis; upper, middle, or distal ureter; and urinary bladder.

*3.2.3 **X-ray characteristics***

Stones can be classified according to plain X-ray appearance [kidney-ureter-bladder (KUB) radiography] (Table 3.6), which varies according to mineral composition [37]. Non-contrast-enhanced computed tomography (NCCT) can be used to classify stones according to density, inner structure, and composition, which can affect treatment decisions (Section 3.3) [36, 37].

Table 3.7: X-ray characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dehydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

3.3 Diagnostic evaluation

*3.3.1 **Diagnostic imaging***

The most appropriate imaging modality will be determined by the clinical situation, which will differ depending on if a ureteral or renal stone is suspected.

Standard evaluation includes a detailed medical history and physical examination. Patients with ureteral stones usually present with loin pain, vomiting, and sometimes fever, but may also be asymptomatic [38]. Immediate evaluation is indicated in patients with solitary kidney, fever or when there is doubt regarding a diagnosis of renal colic. Ultrasound (US) should be used as the primary diagnostic imaging tool, although pain relief, or any other emergency measures, should not be delayed by imaging assessments. Ultrasound is safe (no risk of radiation), reproducible and inexpensive. It can identify stones located in the calyces, pelvis, and pyeloureteric and vesico-ureteral junctions (US with filled bladder), as well as in patients with upper urinary tract (UUT) dilatation. Ultrasound has a sensitivity of 45% and specificity of 94% for ureteral stones and a sensitivity of 45% and specificity of 88% for renal stones [39, 40].

The sensitivity and specificity of KUB is 44-77% [41]. Kidney-ureter-bladder radiography should not be performed if NCCT is being considered [42]; however, it is helpful in differentiating between radiolucent and radiopaque stones and should be used for comparison during follow-up.

3.3.1.1 Evaluation of patients with acute flank pain/suspected ureteral stones

Non-contrast-enhanced computed tomography has become the standard for diagnosing acute flank pain and has replaced intravenous urography (IVU). Non-contrast-enhanced CT can determine stone diameter and density. When stones are absent, the cause of abdominal pain should be identified. In evaluating patients with suspected acute urolithiasis, NCCT is significantly more accurate than IVU or US [43].

Non-contrast-enhanced CT can detect uric acid and xanthine stones, which are radiolucent on plain films, but not indinavir stones [44]. Non-contrast-enhanced CT can determine stone density, inner structure of the stone, skin-to-stone distance, and surrounding anatomy; all of which affect selection of treatment modality [37, 45-47]. The advantage of non-contrast imaging must be balanced against loss of information on renal function and urinary collecting system anatomy, as well as higher radiation dose [48-51].

Radiation risk can be reduced by low-dose CT, which may, however, be difficult to introduce in standard clinical practice [52-56]. In patients with a body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteral stones < 3 mm and 100% for calculi > 3 mm [57]. A meta-analysis (MA) of prospective studies [54] has shown that low-dose CT diagnosed urolithiasis with a pooled sensitivity of 93.1% (95% CI: 91.5-94.4), and a specificity of 96.6% (95% CI: 95.1-97.7%). Dual-energy CT can differentiate uric acid containing stones from calcium-containing stones [58, 59].

Summary of evidence	LE
Non-contrast-enhanced CT is used to confirm stone diagnosis in patients with acute flank pain, as it is superior to IVU.	1a
Enhanced CT enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance.	2a

Recommendations	Strength rating
Immediate imaging is indicated with fever or solitary kidney, and when diagnosis is doubtful.	Strong
Use non-contrast-enhanced computed tomography to confirm stone diagnosis in patients with acute flank pain following initial ultrasound assessment.	Strong
Perform a contrast study if stone removal is planned and the anatomy of the renal collecting system needs to be assessed.	Strong

*3.3.2 **Diagnostics - metabolism-related***

Besides imaging, each emergency patient with urolithiasis needs a succinct biochemical work-up of urine and blood test. At this point, no distinction is made between high- and low-risk patients for stone formation.

3.3.2.1 Basic laboratory analysis - non-emergency urolithiasis patients

Biochemical work-up is similar for all stone patients. However, if no intervention is planned, examination of sodium, potassium, C-reactive protein (CRP), and blood coagulation time can be omitted. Only patients at high risk for stone recurrence should undergo a more specific analytical programme [19]. Stone-specific metabolic evaluation is described in chapter 4.

The easiest method for diagnosing stones is by analysis of a passed stone using a validated method as listed in section 3.3.2.3. Once the mineral composition is known, a potential metabolic disorder can be identified.

3.3.2.2 Analysis of stone composition

Stone analysis should be performed in all first-time stone formers.

In clinical practice, repeat stone analysis is needed in the case of:

- recurrence under pharmacological prevention;
- early recurrence after interventional therapy with complete stone clearance;
- late recurrence after a prolonged stone-free period [60, 61].

Patients should be instructed to filter their urine to retrieve a concrement for analysis. Stone passage and restoration of normal renal function should be confirmed.

The preferred analytical procedures are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [62-64]. Equivalent results can be obtained by polarisation microscopy. Chemical analysis (wet chemistry) is generally deemed to be obsolete [62, 65].

3.3.2.3 Guidelines for laboratory examinations and stone analysis [19, 25, 66, 67]

Recommendations	Strength rating
Urine	
Dipstick test of spot urine sample: • red cells; • white cells; • nitrites; • approximate urine pH; • urine microscopy and/or culture.	Weak
Blood	
Serum blood sample: • creatinine; • uric acid; • (ionised) calcium; • sodium; • potassium; • blood cell count; • C-reactive protein.	Strong

Perform a coagulation test (partial thromboplastin time and international normalised ratio) if intervention is likely or planned.	Strong
Perform stone analysis in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).	Strong
Repeat stone analysis in patients presenting with: • recurrent stones despite drug therapy; • early recurrence after complete stone clearance; • late recurrence after a long stone-free period because stone composition may change.	Strong

*3.3.3 **Diagnosis in special groups and conditions***

3.3.3.1 Diagnostic imaging during pregnancy

In pregnant women radiation exposure may cause non-stochastic (teratogenesis) or stochastic (carcinogenesis, mutagenesis) effects. Teratogenic effects are cumulative with increasing dose and require a threshold dose (< 50 mGy are considered as safe) and depend on the gestation age (minimum risk prior to 8th week and after the 23rd week). Carcinogenesis (doses even < 10 mGy present a risk) and mutagenesis (500-1000 mGy doses are required, far in excess of the doses in common radiographic studies) get worse with increasing dose but they do not require a dose threshold and are not dependent on the gestational age [68].

There is no imaging modality that should be routinely repeated in pregnant women. Scientific societies and organisations agree on the safety of the diagnostic evaluation when US [69], X-ray imaging [70, 71], and MRI [72, 73] are used as and when indicated [74-80]. A radiographic procedure should not be withheld from a pregnant woman if the procedure is clearly indicated and doing so will affect her medical care.

It is generally recommended that an investigation resulting in an absorbed dose to the foetus of greater than 0.5 mGy requires justification.

Ultrasound (when necessary, using changes in renal resistive index and transvaginal/transabdominal US with a full bladder) has become the primary radiological diagnostic tool when evaluating pregnant patients suspected of renal colic. However, normal physiological changes in pregnancy can mimic ureteral obstruction [76-78].

Magnetic resonance imaging can be used, as a second-line option [74], to define the level of urinary tract obstruction, and to visualise stones as a filling defect [72]. As 3 Tesla (T) MRI has not been evaluated in pregnancy, the use of 1.5T is currently recommended [75, 80]. The use of gadolinium is not routinely recommended in pregnancy to avoid toxic effects to the embryo [76].

For the detection of urolithiasis during pregnancy, low-dose CT is associated with a higher positive predictive value (95.8%), compared to MRI (80%) and US (77%). As per White *et al*., low-dose CT offers improved diagnostic accuracy that can avoid negative interventions such as ureteroscopy [81]. Although low-dose CT protocols reduce the radiation exposure, judicious use is currently recommended in pregnant women as a last-line option [76].

Summary of evidence	**LE**
Only low-level data exist for imaging in pregnant women supporting US and MRI.	3

Recommendations	**Strength rating**
Use ultrasound as the preferred method of imaging in pregnant women.	Strong
Use magnetic resonance imaging as a second-line imaging modality in pregnant women.	Strong
Use low-dose computed tomography as a last-line option in pregnant women.	Strong

3.3.3.2 Diagnostic imaging in children

Children with urinary stones have a high risk of recurrence; therefore, standard diagnostic procedures for high-risk patients apply, including a valid stone analysis (section 3.1.3 and chapter 4). The most common non-metabolic disorders facilitating stone formation are vesico-ureteral reflux (VUR), UPJ obstruction, neurogenic bladder, and other voiding difficulties [82].

When selecting diagnostic procedures to identify urolithiasis in children, it should be remembered that these patients might be uncooperative, require anaesthesia, and may be sensitive to ionising radiation. Again, the principle of ALARA (As Low As Reasonably Achievable) should be observed [83-85].

Ultrasound

Ultrasound is the primary imaging technique [86] in children. Its advantages are absence of radiation and no need for anaesthesia. Imaging should include both the fluid-filled bladder with adjoining portion of the ureters, as well

as the upper ureter [87-91]. Colour Doppler US shows differences in the ureteral jet [88] and resistive index of the arciform arteries of both kidneys, which are indicative of the grade of obstruction [89]. Nevertheless, US fails to identify stones in > 40% of children [90-93] and provides limited information on renal function.

Plain films (KUB radiography)
Kidney-ureter-bladder radiography can help to identify stones and their radiopacity and facilitate follow-up.

Intravenous urography
The radiation dose for IVU is comparable to that for voiding cysto-urethrography (0.33 mSV) [94]. However, the need for contrast medium injection is a major drawback.

Non-contrast-enhanced computed tomography
Recent low-dose CT protocols have been shown to significantly reduce radiation exposure [51, 95, 96]. In children, only 5% of stones escape detection by NCCT [88, 96, 97]. Sedation or anaesthesia is rarely needed with modern high-speed CT equipment.

Magnetic resonance urography
Magnetic resonance urography (MRU) cannot be used to detect urinary stones. However, it might provide detailed anatomical information about the urinary collecting system, the location of an obstruction or stenosis in the ureter, and renal parenchymal morphology [98].

3.3.3.2.1 Summary of evidence and guidelines for diagnostic imaging in children

Summary of evidence	**LE**
Ultrasound is the first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder, and the ureter next to the kidney.	2b
A kidney-ureter-bladder radiography (or low-dose NCCT) is an alternative investigation if US will not provide the required information.	2b

Recommendations	**Strength rating**
Complete a metabolic evaluation based on stone analysis in all children.	Strong
Collect stone material for analysis to classify the stone type.	Strong
Perform ultrasound as first-line imaging modality in children when a stone is suspected; it should include the kidney, fluid-filled bladder, and the ureter.	Strong
Perform a kidney-ureter-bladder radiography (or low-dose non-contrast-enhanced computed tomography) if ultrasound will not provide the required information.	Strong

3.4 Disease Management

3.4.1 Renal colic

Pain relief
Non-steroidal anti-inflammatory drugs (NSAIDs) (including metamizoledipyrone), and paracetamol are effective in patients with acute stone colic [99], and have better analgesic efficacy than opioids [100]. Ibuprofen compared to ketorolac is a more rapid acting drug in controlling pain caused by renal colic with a similar side effect profile [101].

Pain relief from intramuscular (i.m.) diclofenac compared favourably with those from intravenous (i.v.) ibuprofen and i.v. ketorolac; however, no recommendation can be given due to the manner in which the results have been reported [102]. The addition of antispasmodics to NSAIDs does not result in better pain control. Patients receiving NSAIDs are less likely to require further analgesia in the short term. It should be taken into consideration that the use of diclofenac and ibuprofen increased major coronary events [99, 100]. Diclofenac is contraindicated in patients with congestive heart failure (New York Heart Association class II-IV), ischaemic heart disease and peripheral arterial- and cerebrovascular disease. Patients with significant risk factors for cardiovascular events should be treated with diclofenac only after careful consideration. As risks increase with dose and duration, the lowest effective dose should be used for the shortest duration [103, 104].

Opioids, particularly pethidine, are associated with a high rate of vomiting compared to NSAIDs and carry a greater likelihood of further analgesia being needed [99, 105]. If an opioid is used, it is recommended that it is not pethidine. Data on other types of non-opioid and non-NSAID medication is increasing. Ketamine in

combination with morphine, compared to morphine alone, leads to morphine consumption reduction, less pain, nausea and vomiting [106-108]. Patients receiving ketamine and NSAIDs attained greater reduction in pain scores with less side effects, and better functional state, as well as less further analgesia requirement than those administered pethidine [109]. However, when comparing ketamine vs. NSAID (ketorolac) alone, equal efficacy but higher rates of dizziness, agitation and hypertension with ketamine were observed [110]. Conflicting results have been reported regarding the utility of i.v. lidocaine. Acupuncture seems to be effective in renal colic alone or in combination, but there is limited data [111, 112].

Prevention of recurrent renal colic

Facilitation of passage of ureteral stones is discussed in Section 3.4.9. For patients with ureteral stones that are expected to pass spontaneously, NSAID tablets or suppositories (e.g., diclofenac sodium, 100-150 mg/day, 3-10 days) may help reduce inflammation and the risk of recurrent pain [113, 114]. Although diclofenac can affect renal function in patients with already reduced function, it has no functional effect in patients with normal renal function [115].

The systematic review and MA by Hollingsworth *et al*., [116] addressed pain reduction as a secondary outcome and concluded that medical expulsive therapy (MET) seems efficacious in reducing pain episodes of patients with ureteral stones.

If analgesia cannot be achieved medically, drainage, using stenting, percutaneous nephrostomy, or stone removal, is indicated [117].

3.4.1.1 Summary of evidence and guidelines for the management of renal coli

Summary of evidence	**LE**
Non-steroidal anti-inflammatory drugs are very effective in treating renal colic and are superior to opioids.	1b
For symptomatic ureteral stones, stone removal as first-line treatment is a feasible option in selected patients.	1b

Recommendations	**Strength rating**
Offer a non-steroidal anti-inflammatory as the first drug of choice e.g., metamizole* (dipyrone); alternatively paracetamol or, depending on cardiovascular risk factors, diclofenac**, indomethacin or ibuprofen***.	Strong
Offer opiates (hydromorphine, pentazocine or tramadol) as a second choice.	Weak
Offer renal decompression or ureteroscopic stone removal in case of analgesic refractory colic pain.	Strong

* *Maximum single oral dose recommended 1000 mg, total daily dose up to 5000 mg, not recommended in the last three months of pregnancy [118].*

** *Affects glomerular filtration rate (GFR) in patients with reduced renal function.*

*** *Recommended to counteract recurrent pain after ureteral colic.*

*3.4.2 **Management of sepsis and/or anuria in obstructed kidney***

The obstructed kidney with all signs of urinary tract infection (UTI) and/or anuria is a urological emergency. Urgent decompression is often necessary to prevent further complications in infected hydronephrosis secondary to stone-induced, unilateral or bilateral, renal obstruction.

Decompression

Currently, there are two options for urgent decompression of obstructed collecting systems:

- placement of an indwelling ureteral stent;
- percutaneous placement of a nephrostomy tube.

There is little evidence to support the superiority of percutaneous nephrostomy over retrograde stenting for primary treatment of infected hydronephrosis. There is no good quality evidence to suggest that ureteral stenting has more complications than percutaneous nephrostomy [119, 120].

Only one RCT [121] compared different modalities of decompression of acute infected hydronephrosis. The complications of percutaneous nephrostomy insertion have been reported consistently, but those of ureteral stent insertion are less well described [119]. Definitive stone removal should be delayed until the infection is cleared following a complete course of antimicrobial therapy. A small RCT showed the feasibility of immediate ureteroscopic stone removal combined with an appropriate antibiotic regimen; however, at the cost of longer hospital stay and higher analgesic requirements [122].

Further measures

Following urgent decompression of the obstructed and infected urinary collecting system, both urine- and blood samples should be sent for culture-antibiogram sensitivity testing and antibiotics should be initiated immediately thereafter or continued, if initiated prior to testing. The regimen should be re-evaluated in the light of the culture-antibiogram results. Although clinically well accepted, the impact of a second antibiogram test on treatment outcome has not yet been evaluated. Intensive care might become necessary [123].

3.4.2.1 Summary of evidence and guidelines for the management of sepsis and anuria

Summary of evidence	LE
For decompression of the renal collecting system, ureteral stents and percutaneous nephrostomy catheters are equally effective.	1b

Recommendations	Strength rating
Urgently decompress the collecting system in case of sepsis with obstructing stones, using percutaneous drainage or ureteral stenting.	Strong
Delay definitive treatment of the stone until sepsis is resolved.	Strong
Collect (again) urine for antibiogram test following decompression.	Strong
Start antibiotics immediately (+ intensive care, if necessary).	Strong
Re-evaluate antibiotic regimen following antibiogram findings.	Strong

*3.4.3 **Medical expulsive therapy***

Several drug classes including α-blockers, calcium channel inhibitors and phosphodiesterase type 5 inhibitors (PDEI-5) are used for MET [124-127]. A class effect of α-blockers in MET has been demonstrated in MAs although this is an off-label indication [128-130]. However, there is contradictory evidence between these studies and several well-designed, multicentre, placebo-controlled, double-blinded randomised studies showing limited, or no, benefit using α-blockers, besides some advantage for distal ureteral stones > 5 mm [131-135]. Based on studies with a limited number of patients [127, 128, 136, 137], no recommendation for the use of PDEI-5 or corticosteroids in combination with α-blockers in MET can be made. The panel concludes that MET using α-blockers seems efficacious in the treatment of patients with distal ureteral stones > 5 mm who are amenable to conservative management. Medical expulsive therapy in special situations is addressed in the relevant chapters.

3.4.3.1 Summary of evidence and guideline for MET

Summary of evidence	LE
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) ureteral stones.	1a
Insufficient data exist to support the use of PDEI-5 or corticosteroids in combination with α-blockers as an accelerating adjunct.	2a
Alpha-blockers increase stone expulsion rates in distal ureteral stones > 5 mm.	1a
A class effect of α-blockers has been demonstrated.	1a

Recommendation	Strength rating
Consider α-blockers for medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong

*3.4.4 **Chemolysis***

Percutaneous irrigation chemolysis

Percutaneous chemolysis is rarely used nowadays, for practical reasons. Percutaneous irrigation chemolysis may be an option for infection-stones and theoretically also for uric acid stones. For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used. The method has been described in case series and literature reviews [138-140].

Oral chemolysis

Stones composed of uric acid, but not sodium or ammonium urate stones, can be dissolved by oral chemolysis. Prior stone analysis may provide information on stone composition. Urinary pH measurement and X-ray characteristics can provide information on the type of stone.

Oral chemolitholysis is based on alkalinisation of urine by application of alkaline citrate or sodium bicarbonate. The pH should be adjusted to 7.0-7.2. Chemolysis is more effective at a higher pH, which might, however, promote calcium phosphate stone formation. Patients will need to adjust the dosage of alkalising medication by self-monitoring the pH of their urine. No RCTs are available for this therapy, which has been in use for decades. Rodman, *et al*., [141] reviewed the principles and provided guidance to its clinical use, which was supported by Becker, *et al*., in 2007 [142] and Elsawy *et al*., in 2019 [143]. Monitoring of radiolucent stones during therapy is the domain of US; however, repeat-NCCT might be necessary [141, 142].

In the case of uric acid obstruction of the collecting system, oral chemolysis in combination with urinary drainage is indicated [144]. A combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones as shown in one RCT for stones > 5 mm [144]. Additional shock wave lithotripsy (SWL) might help to improve the results but evidence is weak [145].

3.4.4.1 Summary of evidence and guidelines for chemolysis

Summary of evidence	**LE**
Irrigation chemolysis has been used in limited clinical settings to dissolve struvite stones.	3
Uric acid stones > 5mm can be dissolved based on oral alkalinisation of the urine above 7.0.	3
For obstructing uric acid stones, a combination of oral chemolysis with tamsulosin is more effective than each substance alone, particularly in stones > 8 mm.	1b

Recommendations (oral chemolysis of uric acid stones)	**Strength rating**
Inform the patient how to monitor urine-pH by dipstick and to modify the dosage of alkalising medication according to urine pH, as changes in urine pH are a direct consequence of such medication.	Strong
Carefully monitor patients during/after oral chemolysis of uric acid stones.	Strong
Combine oral chemolysis with tamsulosin in case of (larger) ureteral stones (if active intervention is not indicated).	Weak

*3.4.5 **Extracorporeal shock wave lithotripsy (ESWL)***

The success of SWL depends on the efficacy of the lithotripter and the following factors:

- size, location (ureteral, pelvic or calyceal), and composition (hardness) of the stones (Section 3.4.9.3);
- patient's habitus (Section 3.4.10.3);
- performance of SWL (best practice, see below).

Each of these factors significantly influences the retreatment rate and final outcome of SWL.

Best clinical practice

Stenting

Routine use of internal stents before SWL does not improve stone free rates (SFRs), nor lowers the number of auxiliary treatments. It may, however, reduce formation of steinstrasse [146-149].

Pacemaker

Patients with a pacemaker can be treated with SWL, provided that appropriate technical precautions are taken. Patients with implanted cardioverter defibrillators must be managed with special care (firing mode temporarily reprogrammed during SWL treatment). However, this might not be necessary with new-generation lithotripters [150].

Shock wave rate

Lowering shock wave frequency from 120 to 60-90 shock waves/min improves SFRs [151-159]. Ultraslow frequency 30 shock waves/min may increase SFR [160]. Tissue damage increases with shock wave frequency [161-164].

Number of shock waves, energy setting and repeat treatment sessions

The number of shock waves that can be delivered at each session depends on the type of lithotripter and shock wave power. There is no consensus on the maximum number of shock waves [165]. Starting SWL on a lower energy setting with stepwise power (and SWL sequence) ramping can achieve vasoconstriction during

treatment [161], which prevents renal injury [166-168]. Animal studies [169] and a prospective randomised study [170] have shown better SFRs (96% vs. 72%) using stepwise power ramping, but no difference has been found for fragmentation or evidence of complications after SWL, irrespective of whether ramping was used [171, 172].

There are no conclusive data on the intervals required between repeated SWL sessions. However, clinical experience indicates that repeat sessions are feasible (within one day for ureteral stones) [173].

Improvement of acoustic coupling

Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important. Defects (air pockets) in the coupling gel deflect 99% of shock waves [174]. Ultrasound gel is probably the most widely-used agent available as a lithotripsy coupling agent [175].

Procedural control

Results of treatment are operator dependent, and experienced clinicians obtain better results. During the procedure, careful imaging control of localisation contributes to outcome quality [176].

Pain Control

Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions [177-180].

Antibiotic prophylaxis

No standard antibiotic prophylaxis before SWL is recommended. However, prophylaxis is recommended in the case of internal stent placement ahead of anticipated treatments and in the presence of increased bacterial burden (e.g., indwelling catheter, nephrostomy tube, or infectious stones) [67, 181, 182].

Medical therapy following ESWL

Despite conflicting results, most RCTs and several MAs support MET after SWL for ureteral or renal stones as adjunct to expedite expulsion and to increase SFRs. Medical expulsion therapy might also reduce analgesic requirements [183-192].

Post-treatment management

Mechanical percussion and diuretic therapy can significantly improve SFRs and accelerate stone passage after SWL [193-196].

Complications of extracorporeal shock wave lithotripsy

Compared to percutaneous nephrolithotomy (PNL) and ureteroscopy (URS), there are fewer overall complications with SWL [197, 198] (Table 3.8). The relationship between SWL and hypertension or diabetes is unclear. Published data are contradictory; however, no evidence exists supporting the hypothesis that SWL may cause long-term adverse effects [199-205].

Table 3.8: Shock wave lithotripsy-related complications [196-210]

Complications			**%**	**Reference**
Related to stone fragments	Steinstrasse		4 – 7	[218-220]
	Regrowth of residual fragments		21 – 59	[207, 208]
	Renal colic		2 – 4	[209]
Infections	Bacteriuria in non-infection stones		7.7 – 23	[207, 210]
	Sepsis		1 – 2.7	[207, 210]
Tissue effect	Renal	Haematoma, symptomatic	< 1	[211]
		Haematoma, asymptomatic	4 – 19	[211]
	Cardiovascular	Dysrhythmia	11 – 59	[207, 212]
		Morbid cardiac events	Case reports	[207, 212]
	Gastrointestinal	Bowel perforation	Case reports	[213-215]
		Liver, spleen haematoma	Case reports	[206, 215-217]

3.4.5.1 *Summary of evidence and guidelines for SWL*

Summary of evidence	LE
Stepwise power ramping prevents renal injury.	1b
Clinical experience has shown that repeat sessions are feasible (within one day for ureteral stones).	4
Optimal shock wave frequency is 1.0 to 1.5 Hz.	1a
Proper acoustic coupling between the cushion of the treatment head and the patient's skin is important.	2
Careful imaging control of localisation of stone contributes to outcome of treatment.	2a
Careful control of pain during treatment is necessary to limit pain-induced movements and excessive respiratory excursions.	1a
Antibiotic prophylaxis is recommended in the case of internal stent placement, infected stones, or bacteriuria.	1a

Recommendations	Strength rating
Ensure correct use of the coupling agent because this is crucial for effective shock wave transportation.	Strong
Maintain careful fluoroscopic and/or ultrasonographic monitoring during shock wave lithotripsy (SWL).	Strong
Use proper analgesia because it improves treatment results by limiting pain-induced movements and excessive respiratory excursions.	Strong
Prescribe antibiotics prior to SWL in the case of infected stones or bacteriuria.	Strong

3.4.6 ***Ureteroscopy (retrograde and antegrade)***

The current standard for rigid ureteroscopes is a tip diameter of < 8 French (F). Rigid URS can be used for the whole ureter [199]. However, technical improvements, as well as the availability of digital scopes, also favour the use of flexible ureteroscopes in the ureter [221].

Percutaneous antegrade removal of ureteral stones is a consideration in selected cases, i.e., large (> 15 mm), impacted proximal ureteral calculi in a dilated renal collecting system [222-224], or when the ureter is not amenable to retrograde manipulation [224-228].

Ureteroscopy for renal stones (RIRS)

Technical improvements including endoscope miniaturisation, improved deflection mechanism, enhanced optical quality and tools, and introduction of disposables have led to an increased use of URS for both renal and ureteral stones. Major technological progress has been achieved for RIRS. A recent systematic review addressing renal stones > 2 cm showed a cumulative SFR of 91% with 1.45 procedures/patient; 4.5% of the complications were > Clavien 3 [221, 229, 230]. Digital scopes demonstrate shorter operation times due to the improvement in image quality [229].

Stones that cannot be extracted directly must be disintegrated. If it is difficult to access stones within the lower renal pole that need disintegration; it may help to displace them into a more accessible calyx [231].

Best clinical practice in ureteroscopy

Access to the upper urinary tract

Most interventions are performed under general anaesthesia, although local or spinal anaesthesia is possible [232]. Intravenous sedation is suitable for female patients with distal ureteral stones [233]. Antegrade URS is an option for large, impacted, proximal ureteral calculi [222-224, 234]. Reduction of flexible ureteroscope diameter may provide similar vision, deflection, and manoeuvrability to standard flexible ureteroscopes potentially with improved ureteric access [235]. Disposable ureteroscopes provides similar safety and clinical effectiveness to reusable scopes. Concerns regarding the cost effectiveness remain [236, 237].

Safety aspects

Fluoroscopic equipment must be available in the operating room. The Panel recommend placement of a safety wire, even though some groups have demonstrated that URS can be performed without it [238-240]. Balloon and plastic dilators should be available, if necessary.

Prior rigid URS can be helpful for optical dilatation followed by flexible URS, if necessary. If ureteral access is not possible, insertion of a JJ stent followed by URS after seven to fourteen days offers an alternative [241]. Bilateral URS during the same session is feasible resulting in equivalent-to-lower SFRs, but slightly higher overall complication rates (mostly minor, Clavien 1 and 2) [242, 243].

Difficult lower pole anatomy such as steep infundibulopelvic angle predisposes to failure during RIRS [244]. Prolonged operative times are linked to increased complication rates in ureteroscopy, and efforts must be made to keep it below 90 minutes [245].

Ureteral access sheaths

Hydrophilic-coated ureteral access sheaths, which are available in different calibres (inner diameter from 9 F upwards), can be inserted (via a guide wire) with the tip placed in the proximal ureter.

Ureteral access sheaths allow easy, multiple, access to the UUT and therefore significantly facilitate URS. The use of ureteral access sheaths improves vision by establishing a continuous outflow, decreases intrarenal pressure, and potentially reduces operating time [246, 247].

The insertion of ureteral access sheaths may lead to ureteral damage, the risk is lowest in presented systems [248]. No data on long-term side effects are available [248, 249]. Whilst larger cohort series showed no difference in SFRs and ureteral damage (stricture rates of about 1.8%), they did show lower post-operative infectious complications [250, 251]. The use of ureteral access sheath is safe and can be useful for large and multiple renal stones or if long procedural time is expected [252].

Stone extraction

The aim of URS is complete stone removal. “Dust and go” strategies should be limited to the treatment of large (renal) stones [253]. Stones can be extracted by endoscopic forceps or baskets. Only baskets made of nitinol can be used for flexible URS [254].

Intracorporeal lithotripsy

The most effective lithotripsy system is the holmium: yttrium-aluminium-garnet (Ho:YAG) laser, which is currently the optimum standard for URS and flexible nephroscopy (Section 3.4.6), because it is effective in all stone types [255, 256]. Compared to low-power lasers, high-power laser reduces procedural time although the reported difference in clinical outcomes were non-significant [257] (J Pneumatic and US systems can be used with high disintegration efficacy in rigid URS [258, 259]). However, stone migration into the kidney is a common problem, which can be prevented by placement of special anti-migration tools proximal of the stone [260]. Medical expulsion therapy following Ho:YAG laser lithotripsy increases SFRs and reduces colic episodes [261]. Thulium fiber laser (TFL) for stone disease has a promising role and offers good clinical outcomes, which seem to be comparable to Ho:YAG laser (holmium) laser. More comparative clinical studies are, however, needed between these two modalities [262, 263].

Stenting before and after URS

Routine stenting is not necessary before URS. However, pre-stenting facilitates ureteroscopic management of stones, improves the SFR, and reduces intra-operative complications [264, 265].

Randomised prospective trials have found that routine stenting after uncomplicated URS (complete stone removal) is not necessary; stenting might be associated with higher post-operative morbidity and costs [266-269]. A ureteral catheter with a shorter indwelling time (one day) may also be used, with similar results [270].

Stents should be inserted in patients who are at increased risk of complications (e.g., ureteral trauma, residual fragments, bleeding, perforation, UTIs, or pregnancy), and in all doubtful cases, to avoid stressful emergencies. The ideal duration of stenting is not known. Most urologists favour one to two weeks after URS. Alpha-blockers reduce the morbidity of ureteral stents and increase tolerability [271, 272].

Medical expulsive therapy before and after ureteroscopy

Medical expulsion therapy before URS might reduce the risk for intra-operative ureteral dilatation, protect against ureteral injury and increase stone free rates four weeks after URS [273].

Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments and reduces episodes of colic [261].

Complications of ureteroscopy

The overall complication rate after URS is 9-25% [199, 274, 275]. Most complications are minor and do not require intervention. There is evidence suggesting a risk of post-operative urosepsis of up to 5% [276, 277]. Ureteral avulsion and strictures are rare (< 1%). Previous perforations, pre-operative positive urine cultures and longer operation time are the most important risk factor for complications [245, 278]. Infectious complications following URS can be minimised using prophylactic antibiotics, limiting stent dwell and procedural time, identification and treatment of UTI, and planning in patients with large stone burden and multiple comorbidities [279].

High intrarenal pressure (IRP) predisposes to URS complications, and measures should be used to reduce IRP. Currently there are no accurate ways to measure intra-operative IRP [280].

3.4.6.1 Summary of evidence and guidelines for retrograde URS, RIRS and antegrade ureteroscopy

Summary of evidence	**LE**
In uncomplicated URS, a post-procedure stent need not be inserted.	1a
In URS (in particular for renal stones), pre-stenting has been shown to improve outcomes.	1b
An α-blocker can reduce stent-related symptoms and colic episodes.	1a
Medical expulsion therapy following Ho:YAG laser lithotripsy accelerates the spontaneous passage of fragments, increases SFRs, and reduces episodes of colic.	1b
The most effective lithotripsy system for flexible ureteroscopy is the Ho:YAG laser.	2a
Pneumatic and US systems can be used with high disintegration efficacy in rigid URS.	2a
Percutaneous antegrade removal of proximal ureter stones, or laparoscopic ureterolithotomy are feasible alternatives to retrograde ureteroscopy, in selected cases.	1b

Recommendations	**Strength rating**
Use holmium: yttrium-aluminium-garnet (Ho:YAG) laser lithotripsy for (flexible) ureteroscopy (URS).	Strong
Perform stone extraction only under direct endoscopic visualisation of the stone.	Strong
Do not insert a stent in uncomplicated cases.	Strong
Offer medical expulsive therapy for patients suffering from stent-related symptoms and after Ho:YAG laser lithotripsy to facilitate the passage of fragments.	Strong
Use percutaneous antegrade removal of ureteral stones as an alternative when shock wave lithotripsy (SWL) is not indicated or has failed, and when the upper urinary tract is not amenable to retrograde URS.	Strong
Use flexible URS in cases where percutaneous nephrolithotomy or SWL are not an option (even for stones > 2 cm). However, in this case there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong

*3.4.7 **Percutaneous nephrolithotomy***

Percutaneous nephrolithotomy remains the standard procedure for large renal calculi. Different rigid and flexible endoscopes are available, and the selection is mainly based on the surgeon's own reference. Standard access tracts are 24-30 F. Smaller access sheaths, < 18 F, were initially introduced for paediatric use, but are now increasingly utilised in the adult population [281, 282].

Contraindications

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL [283].

Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

Best clinical practice

Intracorporeal lithotripsy

Several methods for intracorporeal lithotripsy during PNL are available. Ultrasonic and pneumatic systems are most commonly used for rigid nephroscopy, whilst laser is increasingly used for miniaturised instruments [284]. Flexible endoscopes also require laser lithotripsy to maintain tip deflection, with the Ho:YAG laser having become the standard.

Pre-operative imaging

Pre-procedural imaging evaluations are summarised in Section 3.3.1. In particular, US or CT of the kidney and the surrounding structures can provide information regarding interposed organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung).

Positioning of the patient

Both prone and supine positions are equally safe, although the supine position confers some advantages, it depends on appropriate equipment being available to position the patient correctly, for example, X-ray devices and an operating table. Most studies cannot demonstrate an advantage of supine PNL in terms of operation time. Prone position offers more options for puncture and is therefore preferred for upper pole or multiple accesses [285, 286]. On the other hand, supine position allows simultaneous retrograde access to the collecting system, using flexible ureteroscope (ECIRS) [287].

Puncture

Although fluoroscopy is the most common intra-operative imaging method, the (additional) use of US reduces radiation exposure [288-290]. Pre-operative CT or intra-operative US allows identification of the tissue between the skin and kidney and lowers the incidence of visceral injury. The calyceal puncture may be done under direct visualisation using simultaneous flexible URS [289, 291, 292].

Dilatation

Dilatation of the percutaneous access tract can be achieved using a metallic telescope, single (serial) dilators, or a balloon dilatator. During PNL, safety and effectiveness are similar for different tract dilatation methods [293]. Although there are papers demonstrating that single step dilation is equally effective as other methods and that US only can be used for the dilatation, the difference in outcomes is most likely related to surgeon experience rather than to the technology used [293, 294].

Choice of instruments

The Panel performed a systematic review assessing the outcomes of PNL using smaller tract sizes (< 22 F, mini-PNL) for removing renal calculi [282]. Stone-free rates were comparable in miniaturised and standard PNL procedures. Procedures performed with small instruments tend to be associated with significantly lower blood loss, but the duration of procedure tends to be significantly longer. There were no significant differences in any other complications. However, the quality of the evidence was poor with only two RCTs and the majority of the remaining studies were single-arm case series only. Furthermore, the tract sizes used, and types of stones treated, were heterogeneous; therefore, the risk of bias and confounding were high. There is some evidence of using suction during PNL to reduce intra-renal pressure and increase stone free rate [295].

Nephrostomy and stents

The decision on whether, or not, to place a nephrostomy tube at the conclusion of the PNL procedure depends on several factors, including:

- presence of residual stones;
- likelihood of a second-look procedure;
- significant intra-operative blood loss;
- urine extravasation;
- ureteral obstruction;
- potential persistent bacteriuria due to infected stones;
- solitary kidney;
- bleeding diathesis;
- planned percutaneous chemolitholysis.

Small-bore nephrostomies seem to have advantages in terms of post-operative pain [282, 296, 297]. Tubeless PNL is performed without a nephrostomy tube. When neither a nephrostomy tube nor a ureteral stent is introduced, the procedure is known as totally tubeless PNL [298]. In uncomplicated cases, the latter procedure results in a shorter hospital stay, with no disadvantages reported [299].

Complications of percutaneous nephrolithotomy

A systematic review of almost 12,000 patients shows the incidence of complications associated with PNL; fever 10.8%, transfusion 7%, thoracic complication 1.5%, sepsis 0.5%, organ injury 0.4%, embolisation 0.4%, urinoma 0.2%, and death 0.05% [300].

Peri-operative fever can occur, even with a sterile pre-operative urinary culture and peri-operative antibiotic prophylaxis, because the renal stones themselves may be a source of infection. Intra-operative renal stone culture may therefore help to select post-operative antibiotics [301, 302]. Intra-operative irrigation pressure < 30 mmHg and unobstructed post-operative urinary drainage may be important factors in preventing post-operative sepsis [303]. Bleeding after PNL may be treated by briefly clamping the nephrostomy tube. Super-selective embolic occlusion of the arterial branch may become necessary in the case of severe bleeding.

High intrarenal pressure (IRP) predisposes to PNL complications, and measures should be used to reduce IRP. Currently there are no accurate ways to measure intra-operative intrarenal pressure [280].

3.4.7.1 Summary of evidence and guidelines for endourology techniques for renal stone removal

Summary of evidence	LE
Imaging of the kidney with US or CT can provide information regarding inter-positioned organs within the planned percutaneous path (e.g., spleen, liver, large bowel, pleura, and lung).	1a
Both prone and supine positions are equally safe, but neither has a proven advantage in operating time or SFR.	1a
Percutaneous nephrolithotomy performed with small instruments tends to be associated with significantly lower blood loss, but the duration of procedure tended to be significantly longer. There are no significant differences in SFR or any other complications.	1a
In uncomplicated cases, a totally tubeless PNL results in a shorter hospital stay, with no increase in complication rate.	1a

Recommendations	Strength rating
Perform pre-procedural imaging, including contrast medium where possible or retrograde study when starting the procedure, to assess stone comprehensiveness and anatomy of the collecting system to ensure safe access to the renal stone.	Strong
Perform a tubeless (without nephrostomy tube) or totally tubeless (without nephrostomy tube and ureteral stent) percutaneous nephrolithotomy procedure, in uncomplicated cases.	Strong

*3.4.8 **General recommendations and precautions for stone removal***

3.4.8.1 Antibiotic therapy

Urinary tract infections should always be treated if stone removal is planned. In patients with clinically significant infection and obstruction, drainage should be performed for several days before starting stone removal. A urine culture or urinary microscopy should be performed before treatment [304].

Peri-operative antibiotic prophylaxis

For prevention of infection following URS and percutaneous stone removal, no clear-cut evidence exists [279, 305]. In a review of a large database of patients undergoing PNL, it was found that in patients with negative baseline urine culture, antibiotic prophylaxis significantly reduced the rate of post-operative fever and other complications [306]. Single dose administration was found to be sufficient [307]. Pre-operative prophylactic antibiotics compared to single dose before anaesthesia significantly reduced post-operative sepsis (OR: 0.31, 95% CI: 0.20–0.50; P < 0.00001) and fever (OR: 0.26, 95% CI: 0.14–0.48; P < 0.0001) [301].

Recommendations	Strength rating
Obtain a urine culture or perform urinary microscopy before any treatment is planned.	Strong
Exclude or treat urinary tract infections prior to stone removal.	Strong
Offer peri-operative antibiotic prophylaxis to all patients undergoing endourological treatment.	Strong

3.4.8.2 Antithrombotic therapy and stone treatment

Patients with a bleeding disorder, or receiving antithrombotic therapy, should be referred to an internist for appropriate therapeutic measures before deciding on stone management [308-312]. In patients with an uncontrolled bleeding disorder, the following are at elevated risk of haemorrhage or perinephric haematoma (PNH) (high-risk procedures):

- SWL (hazard ratio of PNH up to 4.2 during anti-coagulant/anti-platelet medication [313-315]);
- PNL;
- percutaneous nephrostomy;
- laparoscopic surgery;
- open surgery [308].

Shock wave lithotripsy is feasible and safe after correction of the underlying coagulopathy [316-320]. In the case of an uncontrolled bleeding disorder or continued antithrombotic therapy, URS in contrast to SWL and PNL, might offer an alternative approach since it is associated with less morbidity [321-323]. Despite

appropriate cessation of anti-platelet agents, following standardised protocols prolonged haematuria in tube drainage after PNL has been reported [324]. Only data on flexible URS are available which support the superiority of URS in the treatment of proximal ureteral stones [325, 326]. Although URS is safe in patients with bleeding disorders or anticoagulation, an individualised patient-approach is necessary [323].

Table 3.9: Risk stratification for bleeding [310-312, 327]

Low-risk bleeding procedures	Cystoscopy Flexible cystoscopy Ureteral catheterisation Extraction of ureteral stent Ureteroscopy
High-risk bleeding procedures	Shock wave lithotripsy Percutaneous nephrostomy Percutaneous nephrolithotomy

Table 3.10: Suggested strategy for antithrombotic therapy in stone removal [310-312]
In collaboration with a cardiologist/internist weigh the risks and benefits of discontinuation of therapy, vs. delaying elective surgical procedures.

Medication/Agent	**Bleeding risk of planned procedure**	**Risk of thromboembolism**		
		Low risk	**Intermediate risk**	**High risk**
Warfarin Dabigatran Rivaroxaban Apixaban	Low-risk procedure	May be continued	Bridging therapy	Bridging therapy
	High-risk procedure	May be temporarily discontinued at appropriate interval. Bridging therapy is strongly recommended.	Bridging therapy	Bridging therapy
Aspirin	Low-risk procedure	Continue	Continue	Elective surgery: postpone. Non deferrable surgery: continue.
	High-risk procedure	Discontinue	Elective surgery: postpone. Non-deferrable surgery: continue, if is possible.	Elective surgery: postpone. Non-deferrable surgery: continue.
Thienopyridine agents (P2Y12 receptor inhibitors)	Low-risk procedure	Discontinue five days before intervention. Resume within 24-72 hours with a loading dose.	Continue	Elective surgery: postpone. Non-deferrable surgery: continue.
	High-risk procedure	Discontinue five days before intervention and resume within 24-72 hours with a loading dose.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours with a loading dose. Bridging therapy -glycoprotein IIb/IIIa inhibitors if aspirin is discontinued.	Elective surgery: postpone. Non-deferrable surgery: discontinue five days before procedure and resume within 24-72 hours, with a loading dose. Bridging therapy -glycoprotein IIb/IIIa inhibitors.

3.4.8.2.1 Summary of evidence and guidelines for antithrombotic therapy and stone treatment

Summary of evidence	LE
Active surveillance is indicated in patients at high risk for thrombotic complications in the presence of an asymptomatic calyceal stone.	4
The temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, should be discussed with the internist.	3
Retrograde (flexible) URS stone removal is associated with less morbidity in patients when antithrombotic therapy cannot be discontinued.	2a

Recommendations	Strength rating
Offer active surveillance to patients at high risk of thrombotic complications in the presence of an asymptomatic calyceal stone.	Weak
Decide on temporary discontinuation, or bridging of antithrombotic therapy in high-risk patients, in consultation with the internist.	Strong
Retrograde (flexible) URS is the preferred intervention if stone removal is essential and antithrombotic therapy cannot be discontinued since it is associated with less morbidity.	Strong

3.4.8.3 Obesity

A high BMI can pose a higher anaesthetic risk and a lower success rate after SWL and PNL and may influence the choice of treatment [328].

3.4.8.4 Stone composition

Stones composed of brushite, calcium oxalate monohydrate, or cystine are particularly hard, as well as homogeneous stones with a high density on NCCT [45, 329]. Percutaneous nephrolithotomy or RIRS and URS are alternatives for removal of large SWL-resistant stones.

Recommendations	Strength rating
Consider the stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit on unenhanced computed tomography.	Strong
Attempt to dissolve radiolucent stones.	Strong

3.4.8.5 Contraindications of procedures

Contraindications of extracorporeal SWL

There are several contraindications to the use of extracorporeal SWL, including:

- pregnancy, due to the potential effects on the foetus [330];
- bleeding disorders, which should be compensated for at least 24 hours before and 48 hours after treatment [331];
- uncontrolled UTIs;
- severe skeletal malformations and severe obesity, which prevent targeting of the stone;
- arterial aneurysm in the vicinity of the stone [332];
- anatomical obstruction distal to the stone.

Contraindications of URS

Apart from general problems, for example with general anaesthesia or untreated UTIs, URS can be performed in all patients without any specific contraindications.

Contraindications of PNL

Patients receiving anti-coagulant therapy must be monitored carefully pre- and post-operatively. Anti-coagulant therapy must be discontinued before PNL [323]. Other important contraindications include:

- untreated UTI;
- tumour in the presumptive access tract area;
- potential malignant kidney tumour;
- pregnancy (Section 3.4.14.1).

General contraindication for endourological procedures
Endourological interventions do not adversely affect renal function although care must be taken in those with poor pre-operative renal function, diabetes and hypertension [333].

3.4.9 ***Specific stone management of ureteral stones***

3.4.9.1 Conservative treatment/observation

There are only limited data regarding spontaneous stone passage according to stone size [334]. It is estimated that 95% of stones up to 4 mm pass within 40 days [199].

Based on an analysis of available evidence, an exact cut-off size for stones that are likely to pass spontaneously cannot be provided [199].

Spontaneous stone passage was reported for 49% of upper ureteral stones, 58% of mid ureteral stones and 68% of distal ureteral stones. Considering stone size almost 75% of stones < 5 mm and 62% of stones ≥ 5 mm passed spontaneously, with an average time to stone expulsion about seventeen days (range 6-29 days) [335]. The Panel is aware of the fact that spontaneous stone expulsion decreases with increasing stone size and that there are differences between individual patients.

Sexual intercourse has been reported to be beneficial in facilitating stone expulsion in men with ureteral stones, in one MA consisting of three RCTs [336].

3.4.9.2 Pharmacological treatment, medical expulsive therapy

Medical expulsive therapy should only be used in informed patients if active stone removal is not indicated. Treatment should be discontinued if complications develop (infection, refractory pain, deterioration of renal function). In case of known uric acid stones in the distal ureter, a combination of alkalinisation with tamsulosin can increase the frequency of spontaneous passage. For details see sections 3.4.3 and 3.4.4.

3.4.9.3 Indications for active removal of ureteral stones

Indications for active removal of ureteral stones are [199, 334, 337]:

- stones with a low likelihood of spontaneous passage;
- persistent pain despite adequate analgesic medication;
- persistent obstruction;
- renal insufficiency (renal failure, bilateral obstruction, or single kidney).

3.4.9.4 Selection of procedure for active removal of ureteral stones

Overall, SFRs after URS or SWL for ureteral stones are comparable. However, larger stones achieve earlier stone-free status with URS. Although URS is effective for ureteral calculi, it has greater potential for complications. However, in the current endourological era, the complication rate and morbidity of URS has been significantly reduced [338]. It has been demonstrated that URS is a safe option in obese patients (BMI > 30 kg/m^2) with comparable SFRs and complication rates. However, in morbidly obese patients (BMI > 35 kg/m^2) the overall complication rates double [339].

The Panel performed a systematic review to assess the benefits and harms of URS compared to SWL [340]. Compared with SWL, URS was associated with a significantly greater SFR of up to four weeks, but the difference was not significant at three months in the included studies. Ureteroscopy was associated with fewer retreatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay. Counterbalancing for URS's higher SFRs, SWL is associated with lower morbidity. Clavien-Dindo grade complications were, if reported, less frequent in patients treated with SWL.

Bleeding disorder
Ureteroscopy can be performed in patients with bleeding disorders, with a moderate increase in complications (see also section 3.4.8.2) [323].

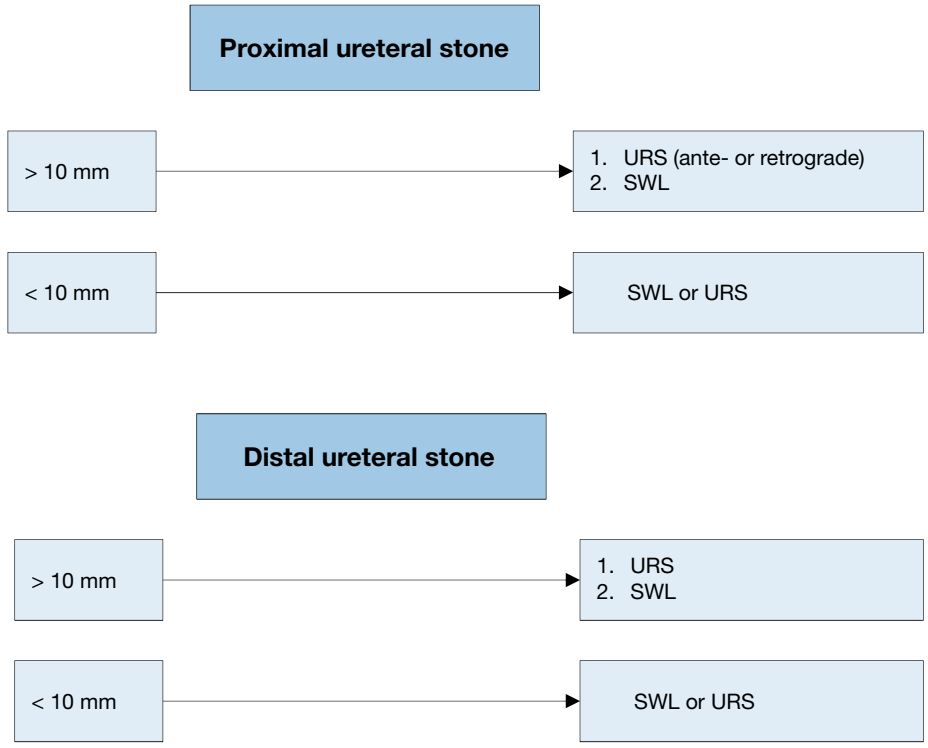
3.4.9.4.1 Summary of evidence and guidelines for selection of procedure for active removal of ureteral stones

Summary of evidence	LE
Observation is feasible in informed patients who develop no complications (infection, refractory pain, deterioration of renal function).	1a
Medical expulsive therapy seems to be efficacious for treating patients with ureteral stones who are amenable to conservative management. The greatest benefit might be among those with > 5 mm (distal) stones.	1a
Compared with SWL, URS was associated with significantly greater SFRs up to four weeks, but the difference was not significant at three months in the included studies.	1a
Ureteroscopy was associated with fewer retreatments and need for secondary procedures, but with a higher need for adjunctive procedures, greater complication rates and longer hospital stay.	1a
In the case of severe obesity, URS is a more promising therapeutic option than SWL.	2b

Recommendations	Strength rating
If active removal is not indicated (section 3.4.9.3) in patients with newly diagnosed small* ureteral stones, observe patient initially with periodic evaluation.	Strong
Offer α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong
Inform patients that ureteroscopy (URS) has a better chance of achieving stone-free status with a single procedure.	Strong
Inform patients that URS has higher complication rates when compared to shock wave lithotripsy.	Strong
Use URS as first-line therapy for ureteral (and renal) stones in cases of severe obesity.	Strong

**See stratification data [199].*

Figure 3.1: Treatment algorithm for ureteral stones (if active stone removal is indicated)



SWL = shock wave lithotripsy; URS = Ureteroscopy.

3.4.10 ***Specific stone management of renal stones***

The natural history of small, non-obstructing asymptomatic calculi is not well defined, and the risk of progression is unclear. There is still no consensus on the follow-up duration, timing, and type of intervention. Treatment options are chemolysis or active stone removal.

3.4.10.1 Conservative treatment (observation)

Observation of renal stones, especially in calyces, depends on their natural history (section 3.4.10.3). The recommendations provided are not supported by high-level literature [341]. There is a prospective trial supporting annual observation for asymptomatic inferior calyceal stones, < 10 mm. In case stone growth is detected, the follow-up interval should be lowered. Intervention is advised for growing stones > 5 mm [342]. In a systematic review of patients with asymptomatic renal stones on active surveillance spontaneous stone passage rates varied from 3-29%, symptom development from 7-77%, stone growth from 5-66%, surgical intervention from 7-26% [341].

3.4.10.2 Pharmacological treatment of renal stones

Dissolution of stones through pharmacological treatment is an option for uric acid stones only, but information on the composition of the stone will need to guide the type of treatment selected. See sections 3.4.4. and 3.4.8.4.

3.4.10.3 Indications for active stone removal of renal stones

Indications for the removal of renal stones, include:

- stone growth;
- stones in high-risk patients for stone formation;
- obstruction caused by stones;
- infection;
- symptomatic stones (e.g., pain or haematuria) [343];
- stones > 15 mm;
- stones < 15 mm if observation is not the option of choice;
- patient preference;
- comorbidity;
- social situation of the patient (e.g., profession or travelling);
- choice of treatment.

The risk of a symptomatic episode or need for intervention in patients with asymptomatic renal stones seems to be ~10-25% per year, with a cumulative five-year event probability of 48.5% [342, 344, 345]. A prospective RCT with more than two years clinical follow-up reported no significant difference between SWL and observation when comparing asymptomatic calyceal stones < 15 mm in terms of SFR, symptoms, requirement for additional treatment, quality of life (QoL), renal function, or hospital admission [346]. Although some have recommended prophylaxis for these stones to prevent renal colic, haematuria, infection, or stone growth, conflicting data have been reported [345, 347, 348]. In a follow-up period of almost five years after SWL, two series have demonstrated that up to 25% of patients with small residual fragments needed treatment [208, 349]. Although the question of whether calyceal stones should be treated is still unanswered, stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment [343, 350, 351].

3.4.10.4 Selection of procedure for active removal of renal stones

For general recommendations and precautions see section 3.4.8.

3.4.10.4.1 Stones in renal pelvis or upper/middle calyces

Shock wave lithotripsy, PNL and RIRS are available treatment modalities for renal calculi. While PNL efficacy is hardly affected by stone size, the SFRs after SWL or URS are inversely proportional to stone size [352-355]. Shock wave lithotripsy achieves good SFRs for stones up to 20 mm, except for those at the lower pole [354, 356, 357]. Endourology is considered an alternative because of the reduced need for repeated procedures and consequently a shorter time until stone-free status is achieved. Stones > 20 mm should be treated primarily by PNL, because SWL often requires multiple treatments, and is associated with an increased risk of ureteral obstruction (colic or steinstrasse) with a need for adjunctive procedures (Figure 3.2) [197]. Retrograde renal surgery cannot be recommended as first-line treatment for stones > 20 mm in uncomplicated cases as SFRs decrease, and staged procedures will be required [358-360]. However, it may be a first-line option in patients where PNL is not an option or contraindicated.

3.4.10.4.2 Stones in the lower renal pole

The stone clearance rate after SWL seems to be lower for stones in the inferior calyx than for other intra-renal locations. Although the disintegration efficacy of SWL is not limited compared to other locations, the fragments often remain in the calyx and cause recurrent stone formation. The reported SFR of SWL for lower pole calculi is 25-95%. The preferential use of endoscopic procedures is supported by some current reports, even for stones < 1 cm [197, 352, 353, 355, 356, 360-373].

The following can impair successful stone treatment by SWL [363, 374-379]:

- steep infundibular-pelvic angle;
- long calyx;
- long skin-to-stone distance;
- narrow infundibulum;
- shock wave-resistant stones (calcium oxalate monohydrate, brushite, or cystine).

Further anatomical parameters cannot yet be established. Supportive measures such as inversion, vibration or hydration may facilitate stone clearance (See section 3.4.5 ESWL) [194, 196, 380].

If there are negative predictors for SWL, PNL and RIRS might be reasonable alternatives, even for smaller calculi [361]. Retrograde renal surgery seems to have comparable efficacy to SWL [197, 353, 356, 381]. Recent clinical experience has suggested a higher SFR of RIRS compared to SWL, but at the expense of greater invasiveness. Depending on operator skills, stones up to 3 cm can be treated by RIRS [230, 382-384]. However, staged procedures are frequently required.

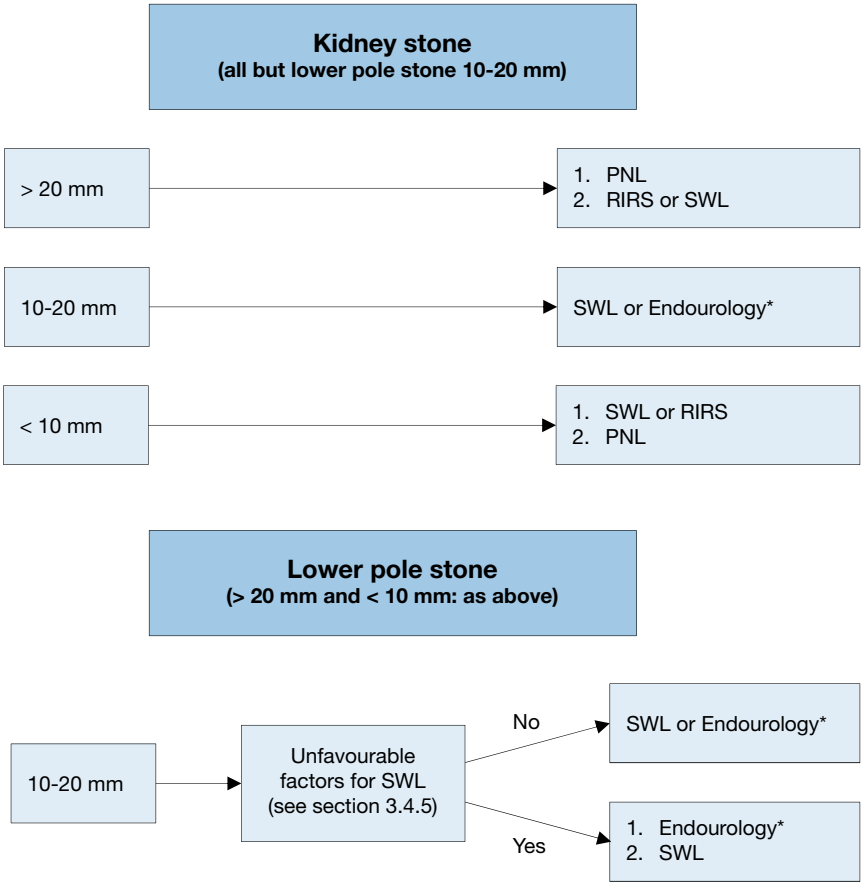
In complex stone cases, open or laparoscopic approaches are possible alternatives although they are infrequently used.

3.4.10.5 Summary of evidence and guidelines for the management of renal stones

Summary of evidence	**LE**
It is still debatable whether renal stones should be treated, or whether annual follow-up is sufficient for asymptomatic calyceal stones that have remained stable for six months.	4
Although the question of whether asymptomatic calyceal stones should be treated is still unanswered, stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain are indications for treatment.	3
Percutaneous nephrolithotomy is indicated in renal stones > 2 cm as primary option.	1a

Recommendations	**Strength rating**
Follow-up periodically in cases where renal stones are not treated (initially after six months then yearly, evaluating symptoms and stone status, either by ultrasound, kidney-ureter bladder radiography or computed tomography [CT]).	Strong
Offer active treatment for renal stones in case of stone growth, *de novo* obstruction, associated infection, and acute and/or chronic pain.	Weak
Evaluate stone composition before deciding on the method of removal, based on patient history, former stone analysis of the patient or Hounsfield unit (HU) on unenhanced CT. Stones with density > 1,000 HU (and with high homogeneity) on non-contrast-enhanced CT are less likely to be disintegrated by shock wave lithotripsy (SWL).	Strong
Perform percutaneous nephrolithotomy (PNL) as first-line treatment of larger stones > 2 cm.	Strong
Treat larger stones (> 2 cm) with flexible ureteroscopy or SWL, in cases where PNL is not an option. However, in such instances there is a higher risk that a follow-up procedure and placement of a ureteral stent may be needed.	Strong
Perform PNL or retrograde intrarenal surgery for the lower pole, even for stones > 1 cm, as the efficacy of SWL is limited (depending on favourable and unfavourable factors for SWL).	Strong

Figure 3.2: Treatment algorithm for renal stones (if/when active treatment is indicated)



**The term 'Endourology' encompasses all PNL and URS interventions.*
PNL = percutaneous nephrolithotomy; RIRS = retrograde intrarenal surgery; SWL = shock wave lithotripsy; URS = ureteroscopy.

3.4.11 Laparoscopy and open surgery

Advances in SWL and endourological surgery (URS and PNL) have significantly decreased the indications for open or laparoscopic stone surgery [385-390]. There is a consensus that most complex stones, including partial and complete staghorn stones, should be approached primarily with PNL. Additionally, a combined approach with PNL and RIRS may also be an appropriate alternative. However, if percutaneous approaches are not likely to be successful, or if multiple endourological approaches have been performed unsuccessfully; open or laparoscopic surgery may be a valid treatment option [391-397].

Few studies have reported laparoscopic stone removal. These procedures are usually reserved for special cases. When expertise is available, laparoscopic ureterolithotomy can be performed for large proximal ureteral stones as an alternative to URS or SWL [398, 399]. These more invasive procedures have yielded high SFRs and lower auxiliary procedure rates [223, 234, 400]. A recent systematic review showed no difference in the post-operative phase for stented or unstented laparoscopic ureterolithotomy [400].

Laparoscopic pyelolithotomy could be offered for solitary stones > 2 cm located in renal pelvis as an alternative to PNL [401]. In addition, in selected cases with an extrarenal and dilated pelvis, RLP can be considered as an alternative management of staghorn calculi [402].

A few studies with limited numbers of patients have reported using robotic surgery in the treatment of urinary stones [403]. Open surgery should be considered as the last treatment option, after all other possibilities have been explored.

Studies on laparoscopy should be interpreted with caution due to their weak design and low quality of evidence.

3.4.11.1 Summary of evidence and guideline for laparoscopy and open surgery

Recommendation	Strength rating
Offer laparoscopic or open surgical stone removal in rare cases in which shock wave lithotripsy, retrograde or antegrade ureteroscopy and percutaneous nephrolithotomy fail, or are unlikely to be successful.	Strong

*3.4.12 **Steinstrasse***

Steinstrasse is an accumulation of stone fragments or stone gravel in the ureter and may interfere with the passage of urine [404]. Steinstrasse occurs in 4-7% cases of SWL [218], and the major factor in the development of steinstrasse formation is stone size [405].

A major problem of steinstrasse is ureteral obstruction, which may be silent in up to 23% of cases. A MA including eight RCTs (n = 876) suggested a benefit of stenting before SWL in terms of steinstrasse formation, but did not result in a benefit on SFRs or less auxiliary treatments [147]. When steinstrasse is asymptomatic, conservative treatment is an initial option. Medical expulsion therapy increases stone expulsion and reduces the need for endoscopic intervention [406, 407]. Ureteroscopy and SWL are effective in treatment of steinstrasse [220, 408]. In the event of UTI or fever, the urinary system should be decompressed, preferably by percutaneous nephrostomy [120, 122].

3.4.12.1 Summary of evidence and guidelines for steinstrasse

Summary of evidence	LE
Medical expulsion therapy increases the stone expulsion rate of steinstrasse.	1b
Ureteroscopy is effective for the treatment of steinstrasse.	3
Only low-level evidence is available, supporting SWL or URS for the treatment of steinstrasse.	4

Recommendations	Strength rating
Treat steinstrasse associated with urinary tract infection (UTI)/fever preferably with percutaneous nephrostomy.	Weak
Treat steinstrasse when large stone fragments are present with shock wave lithotripsy or ureteroscopy (in absence of signs of UTI).	Weak

*3.4.13 **Management of patients with residual stones***

Following initial treatment with SWL, URS or PNL, residual fragments may remain and require additional intervention [349, 409, 410]. Most of the studies indicate that initial imaging is performed on the first day or the first week after treatment. However, false positive results from dust or residual fragments, that will pass spontaneously without causing any stone-related event, might lead to over-treatment. Therefore, imaging at four weeks seems most appropriate [411-413]. Compared to US, KUB and IVU, NCCT scan has a higher sensitivity to detect small residual fragments after definitive treatment of ureteral or kidney stones [414, 415]. However, more than half of the patients with a residual fragment on NCCT images may not experience a stone-related event [416].

It is clear that NCCT has the highest sensitivity to detect residual fragments; however, this must be balanced against the increased detection of clinically insignificant fragments and the exposure to ionising radiation when compared with KUB and US. In the absence of high-level supporting evidence, the timing of follow-up imaging studies and need for secondary intervention is left to the discretion of the treating physician. Recurrence risk in patients with residual fragments after treatment of infection stones is higher than for other stones [417]. For all stone compositions, 21-59% of patients with residual stones required treatment within five years. Fragments > 5 mm are more likely than smaller ones to require intervention [208, 418, 419]. There is evidence that fragments > 2 mm are more likely to grow, although this is not associated with increased re-intervention rates at one year follow-up [409].

3.4.13.1 Summary of evidence and guideline for management of patients with residual stones

Summary of evidence	LE
To detect residual fragments after SWL, URS or PNL, deferred imaging is more appropriate than immediate imaging post intervention.	3

Recommendation	Strength rating
Perform imaging after shock wave lithotripsy, ureteroscopy or percutaneous antegrade ureteroscopy to determine presence of residual fragments.	Strong

3.4.14 ***Management of specific patient groups***

3.4.14.1 Management of urinary stones and related problems during pregnancy

Clinical management of a pregnant urolithiasis patient is complex and demands close collaboration between patient, radiologist, obstetrician, and urologist. For diagnostic imaging see section 3.3.1.

If spontaneous passage does not occur, or if complications develop (e.g., intractable symptoms, severe hydronephrosis, spontaneous renal fornix rupture [420] or induction of premature labour), placement of a ureteral stent or a percutaneous nephrostomy tube is necessary as it is more effective than conservative treatment for symptom relief [421-423].

Unfortunately, these temporising therapies are often associated with poor tolerance, and they require multiple exchanges during pregnancy, due to the potential for rapid encrustation [424].

Ureteroscopy has become a reasonable alternative in these situations [413, 425]. When compared to temporary ureteral JJ stenting until after delivery, ureteroscopy resulted in fewer needs for stent exchanges, less irritative LUTS and better patient satisfaction [426].

Non-urgent ureteroscopy in pregnant women is best performed during the second trimester by an experienced urologist. Counselling of the patient should include access to neonatal and obstetric services [76].

Although feasible, percutaneous removal of renal stones during pregnancy remains an individual decision and should be performed only in experienced centres [427]. Pregnancy remains an absolute contraindication for SWL.

3.4.14.1.1 Summary of evidence and guideline for the management of urinary stones and related problems during pregnancy

Summary of evidence	LE
Stent insertion seems to be more effective than conservative treatment in the management of symptomatic moderate-to-severe hydronephrosis during pregnancy.	1a
Ureteroscopy is a reasonable alternative to avoid long-term stenting/drainage.	1b
There is a higher tendency for stent encrustation during pregnancy.	3

Recommendation	Strength rating
Treat all uncomplicated cases of urolithiasis in pregnancy conservatively (except when there are clinical indications for intervention).	Strong

3.4.14.2 Management of stones in patients with urinary diversion

Aetiology

Patients with urinary diversion are at high risk for stone formation in the renal collecting system and ureter or in the conduit or continent reservoir [428, 429]. Metabolic factors (hypercalciuria, hyperoxaluria and hypocitraturia), infection with urease-producing bacteria, foreign bodies, mucus secretion, and urinary stasis are responsible for stone formation [430] (section 3.1.3). One study has shown that the risk for recurrent upper tract stones in patients with urinary diversion subjected to PNL was 63% at five years [431].

Management

Smaller upper-tract stones can be treated effectively with SWL [227, 432]. In the majority of cases, endourological techniques are necessary to achieve stone-free status [225]. In individuals with long, tortuous conduits or with

invisible ureter orifices, a retrograde endoscopic approach might be difficult or impossible [433].

For stones in the conduit, a trans-stomal approach can be used to remove all stone material (along with the foreign body) using standard techniques, including intracorporeal lithotripsy and flexible endoscopes. Trans-stomal manipulations in continent urinary diversion must be performed carefully to avoid disturbance of the continence mechanism [434].

Before considering any percutaneous approach in these cases, CT should be undertaken to assess the presence of overlying bowel, which could make this approach unsafe [435], and if present, an open surgical approach should be considered.

Prevention

Recurrence risk is high in these patients [431]. Metabolic evaluation and close follow-up are necessary to obtain the risk parameters for effective long-term prevention. Preventive measures include medical management of metabolic abnormalities, appropriate therapy of urinary infections, and hyperdiuresis or regular irrigation of continent reservoirs [436].

3.4.14.2.1 Summary of evidence and guideline for the management of stones in patients with urinary diversion

Summary of evidence	**LE**
The choice of access depends on the feasibility of orifice identification in the conduit or bowel reservoir. Whenever a retrograde approach is impossible, percutaneous access with antegrade ureteroscopy is the alternative.	4

Recommendation	**Strength rating**
Perform percutaneous lithotomy to remove large renal stones in patients with urinary diversion, as well as for ureteral stones that cannot be accessed via a retrograde approach, or that are not amenable to shock wave lithotripsy.	Strong

3.4.14.3 Management of stones in patients with neurogenic bladder

Aetiology, clinical presentation and diagnosis

Patients with neurogenic bladder develop urinary calculi because of additional risk factors such as bacteriuria, hydronephrosis, VUR, renal scarring and lower urinary tract reconstruction [437]. The most common causes are urinary stasis and infection (section 3.1.3). Indwelling catheters and surgical interposition of bowel segments for treatment of bladder dysfunction both facilitate UTI. Although calculi can form at any level of the urinary tract, they occur more frequently in the bladder; especially if bladder augmentation has been performed [438, 439].

Diagnosis of stones may be difficult and delayed in the absence of clinical symptoms due to sensory impairment and vesico-urethral dysfunction. Difficulties in self-catheterisation should lead to suspicion of bladder calculi. Imaging studies are needed (US, CT) to confirm the clinical diagnosis prior to surgical intervention.

Management

Management of calculi in patients with neurogenic bladder is similar to that described in section 3.3.3. In myelomeningocele patients, latex allergy is common; therefore, appropriate measures need to be taken regardless of the treatment [440]. Any surgery in these patients must be performed under general anaesthesia because of the impossibility of using spinal anaesthesia. Bone deformities often complicate positioning on the operating table [441]. The risk of stone formation after augmentation cystoplasty in immobile patients with sensory impairment can be significantly reduced by irrigation protocols [436].

For efficient long-term stone prevention in patients with neurogenic bladder, correction of the metabolic disorder, appropriate infection control, and restoration of normal storing/voiding function of the bladder are needed.

3.4.14.3.1 Summary of evidence and guideline for the management of stones in patients with neurogenic bladder

Summary of evidence	**LE**
Patients undergoing urinary diversion and/or suffering from neurogenic bladder dysfunction are at risk for recurrent stone formation.	3
In myelomeningocele patients, latex allergy is common.	2

Recommendation	Strength rating
Take appropriate measures regardless of the treatment provided since in myelomeningocele patients latex allergy is common.	Strong

3.4.14.4 Management of stones in patients with transplanted kidneys

Stones in transplanted kidneys can either be transplanted or present *de novo* allograft stones. Usually they are detected by routine US examination, followed by NCCT in cases of unclear diagnosis [442].

Aetiology

Transplant patients depend on their solitary kidney for renal function. Impairment causing urinary stasis/obstruction therefore requires immediate intervention or drainage of the transplanted kidney. Stones in kidney allografts have an incidence of 1% [443]. Risk factors for *de novo* stone formation in these patients are multi-fold:

- Immunosuppression increases the infection risk, resulting in recurrent UTIs.
- Hyper-filtration, excessively alkaline urine, renal tubular acidosis (RTA), and increased serum calcium caused by persistent tertiary hyperparathyroidism [444] are biochemical risk factors.

Management

Selecting the appropriate technique for stone removal in a transplanted kidney is difficult, although management principles are similar to those applied in other single renal units [445-447]. Additional factors such as transplant function, coagulative status, and anatomical obstacles due to the iliacal position of the organ directly influence the surgical strategy.

For large or ureteral stones, careful percutaneous access and subsequent antegrade endoscopy are more favourable. The introduction of small flexible ureteroscopes and the holmium laser has made URS a valid treatment option for transplant calculi; however, one must be aware of potential injury to adjacent organs [446, 448, 449]. Retrograde access to transplanted kidneys is difficult due to the anterior location of the ureteral anastomosis, and ureteral tortuosity [450-452].Treatment of donor stones may be needed pre-transplant and increases the pool available for renal transplants. Post-transplant stone disease may also need treatment to maintain the allograft function. A systematic review evaluating the outcomes of pre- vs. post-transplant URS demonstrated a 100% SFR with an overall 7.5% complication rate, compared to SFR of 60-100% with an overall complication rate of 12.9% for post-transplant URS; most complications were Clavien 1 [453].

3.4.14.4.1 Summary of evidence and guideline for the management of stones in patients with transplanted kidneys

Summary of evidence	LE
Conservative treatment for small asymptomatic stones is only possible under close surveillance and in absolutely compliant patients.	3
Shock wave lithotripsy for small calyceal stones is an option with minimal risk of complication, but localisation of the stone can be challenging and SFRs are poor.	4

Recommendation	Strength rating
Offer patients with transplanted kidneys, any of the contemporary management options, including shock wave lithotripsy, flexible ureteroscopy and percutaneous nephrolithotomy.	Weak

3.4.14.5 Special problems in stone removal

Table 3.11: Special problems in stone removal

Calyceal diverticulum stones	• SWL, PNL [454] (if possible) or RIRS [454, 455]. • Can also be removed using laparoscopic retroperitoneal surgery [456, 457]. • Patients may become asymptomatic due to stone disintegration (SWL), whilst well-disintegrated stone material remains in the original position due to narrow calyceal neck.
Horseshoe kidneys	• Can be treated in line with the options described above [458]. • Passage of fragments after SWL might be poor. • Acceptable SFRs (up to 76%) with low major complication rates (2.4%) can be achieved with flexible ureteroscopy [459, 460].
Stones in pelvic kidneys	• SWL, RIRS, PNL or laparoscopic surgery [461].

Stones formed in a continent reservoir	• Each stone must be considered and treated individually.
Patients with obstruction of the UPJ	• When outflow abnormality requires correction, stones can be removed by PNL together with percutaneous endopyelotomy or open/laparoscopic reconstructive surgery. • URS together with endopyelotomy with Ho:YAG laser. • Incision with an Acucise® balloon catheter might be considered, provided the stones can be prevented from falling into the pelvic-ureteral incision [462-465]. • Open surgery with correction of the UPJ obstruction (pyeloplasty) and stone removal is a feasible option [466].

*3.4.15 **Management of stones in children***

The true incidence of nephrolithiasis in children remains unclear due to the global lack of large epidemiological studies. Data derived from nationwide epidemiological studies, studies performed in different counties worldwide [467] and large-scale databases [468, 469] indicate that the incidence and prevalence of paediatric urinary stone disease has increased over the last few decades. Although boys are most commonly affected in the first decade of life [470] the greatest increase in incidence has been seen in older female adolescences [467].

Stone composition is similar in children as in adults, with a predominance of calcium oxalate stones. Compared to historical data, metabolic abnormalities responsible for stone formation are less commonly identified in children nowadays [471-473]. Hypocitraturia, low urine volume and hypercalciuria predominate [85, 471-473]. Age may affect the predominant metabolic abnormality with hypercalciuria and hypocitraturia being the most common disorder present in children < 10 and > 10 years old, respectively [473]. Genetic or systemic diseases (e.g., cystinuria or nephrocalcinosis) contributing to stone formation are relatively frequent in children accounting for less than 17% of the identifying causes [471, 474]. The role of diet remains unclear in children, although there is some evidence that children are drinking less water and taking greater daily amounts of sodium than is recommended [475-477].

For diagnostic procedures see section 3.3.3.2, for acute decompression see section 3.4.2. and for metabolic evaluation see chapter 4.

3.4.15.1 Clinical presentation

Children with urinary stones can be asymptomatic or present with non-specific symptoms that necessitate a high index of suspicion for proper diagnosis. Symptoms are age-dependent with infants presenting with crying, irritability and vomiting in 40% of cases [478] while in older children flank pain, micro or gross haematuria and recurrent UTIs are more common [479].

3.4.15.2 Conservative management

There is a lack of evidence on conservative management of paediatric stones with evidence for ureteric calculi coming from the placebo arms of medical expulsive trials, while evidence for renal stones comes from small cohort studies, either on primary stones [480, 481] or residual fragments remained after SWL, RIRS or PNL [482]. Expectant management for single, asymptomatic lower-pole renal stones could be the initial approach with increased odds of stone passage, especially in patients with non-struvite, non-cystine stones < 7 mm, with no anatomic abnormalities [480]. Intervention may be needed for stones located elsewhere independently of their size [480-482].

3.4.15.3 Medical expulsive therapy in children

There are limited studies on MET as off-label expulsive therapy for children with stones which show conflicting outcomes. A recent MA of five trials showed that adrenergic α-antagonists (tamsulosin 0.2-0.4 mg/day and doxazosin 0.03 mg/kg/day) are effective for MET increasing SFR compared to control (OR = 2.7, p = 0.001) without significantly increasing the treatment-emergent adverse events (OR = 2.01, p = 0.17) [483]. Similarly, an updated systematic review of six placebo-controlled studies showed that α-blockers might increase SFR of distal ureteric stones (RR: 1.34, 95% CI: 1.16 - 1.54) [484]. Due to study limitations and very serious imprecision, no conclusion could be drawn regarding the effect of MET on hospital stay, pain episodes or secondary procedures for residual fragments after definitive stone treatment [484].

3.4.15.4 Extracorporeal shock wave lithotripsy

Shock wave lithotripsy is still the first-line treatment for most ureteral stones in children. However, it is less likely to be successful for stones > 10 mm in diameter, impacted stones, calcium oxalate monohydrate or cystine stones, or for stones in children with unfavourable anatomy and in whom localisation is difficult [485].

Studies on extracorporeal SWL in children suggest an overall SFR of 70-90%, retreatment rate of 4-50% and need for auxiliary procedures in 4-12.5% of cases [486-490]. A MA of fourteen studies reporting on 1,842 paediatric patients treated with SWL found significantly higher SFR for stones < 10 mm than for stones > 10 mm and higher retreatment rates as the stone size increased [485]. For best clinical practice see section 3.4.5. A recent MA on slow SWL vs. rapid SWL for renal stones revealed very low-quality evidence about the effects of SWL on SFRs, serious adverse events or complications of treatment and secondary procedures for residual fragments [484]. Shock wave lithotripsy is well tolerated; however, good treatment outcomes are more likely to require the administration of general anaesthesia to children. With improvements in modern (second and third generation) lithotripters, successful treatment using intravenous sedation, patient-controlled analgesia or no medication at all has been increasingly performed in a select population of older, co-operative children [491].

Based on the results of a recent MA which compared SWL to dissolution therapy for intra-renal stones, and SWL to ureteroscopy with holmium laser or pneumatic lithotripsy for renal and distal ureteric stones, no firm conclusions can be drawn about the effects of SWL on SFR, serious adverse events or complications of treatment and secondary procedures for residual fragments [484]. When SWL was compared to mini-percutaneous nephrolithotomy for lower pole renal stones 1-2 cm in size SWL resulted in lower SFRs (RR: 0.88, 95% CI: 0.80 - 0.97; moderate-quality evidence) and higher rates of secondary procedures (RR: 2.50, 95% CI: 1.01 - 6.20; low-quality evidence); however, SWL showed less severe adverse events (RR: 0.13, 95% CI: 0.02 - 0.98; low-quality evidence) [492].

3.4.15.5 Endourological procedures

Rigid/semi-rigid ureteroscopy

In recent years ureteroscopy is increasingly used in children with ureteral stones [493]. Ureteroscopy proved to be effective with SFR of 81-98% [494-496], retreatment rates of 6.3%-10% [497] and complication rates of 1.9-23% [494-496, 498]. Similar to adults, routine stenting is not necessary before URS. Pre-stenting may facilitate URS, increase SFR and decrease complication rates [499, 500].

Flexible ureteroscopy/retrograde intrarenal surgery

Retrograde intra-renal surgery with flexible ureteroscopes (FURS) has become an efficacious treatment modality for paediatric renal stones. Recent studies report SFRs of 76-100%, retreatment rates of 0-19% and complication rates of 0-28% [501-504]. Younger age, cystine composition [505], large stone diameter [504] and lack of pre-stenting predispose to FURS failure in children [499].

Although high-level evidence is lacking to support a strong recommendation [484], FURS may be a particularly effective treatment option for lower calyceal stones in the presence of unfavourable factors for SWL [496, 502, 506].

For large and complex kidney stones RIRS has a significantly lower SFR compared to PNL (71% vs. 95%), but is associated with less radiation exposure, lower complication rates and a shorter hospital stay [507]. Similarly, retrospectively data indicate that RIRS may achieve lower SFRs compared to minor micropercutaneous surgery in favour of shorter operative time, shorter fluoroscopy time, and less hospitalisation time [508, 509]. A recently published MA confirmed these results [510].

Percutaneous nephrolithotomy

Indications for PNL in children are similar to those in adults, and include renal stones > 2 cm, or smaller stones resistant to SWL and ureteroscopic treatment. Reported SFRs with paediatric PNL are 71.4-95% after a single session [507-509, 511, 512] with an overall complication rate of 20% [513]. High degree of hydronephrosis, increased number of tracts and operative time [514] and large tract size [512, 515-517] are associated with increased blood loss. Child age [516] and stone burden [512] predispose to the use of larger instruments during PNL in children. Miniaturisation of equipment increases the opportunity to perform tubeless PNL in appropriately selected children, which can reduce the length of hospital stay and post-operative pain [518, 519].

Concerns have been raised regarding possible adverse effects of PNL on the renal parenchyma of the developing child. However, focal damage is only reported in 5% of cases [520]. Using pre- and post-PNL dimercaptosuccinic acid (DMSA) scans, Cicekbilek *et al*., demonstrated that PNL tracts between 12-24 Charrière in size did not cause significant harm to paediatric kidneys [511].

3.4.15.6 Open and laparoscopic/robot-assisted stone surgery

With the advances in ESWL, PNL and RIRS, very few cases of paediatric urolithiasis require open surgery. Data extracted from the National Inpatient Sample (NIS) databases for 2001-2014 showed that in the USA incisional procedures (mainly nephrolithotomy, pyelolithotomy and ureterotomy) were performed in 2.6% of hospitalised patients (52% aged 15-17 years) who required surgical intervention for urinary stones [521]. Laparoscopy

for the management of paediatric renal and ureteric stones is a safe and effective procedure when specific indications are followed. Stone free rates of 100% were reported when laparoscopic pyelolithotomy was applied for a > 1 cm single stone located in an extra-renal pelvis [522], or when laparoscopic ureterolithotomy was applied to impacted ureteric stones ≥ 1.5 cm, or to ureteric stones that were refractory to SWL or URS [523]. There are extremely limited data available on efficacy and complications of robot-assisted laparoscopic management of paediatric urolithiasis [524].

3.4.15.7 Special considerations on recurrence prevention

All paediatric stone formers need metabolic evaluation and recurrence prevention with respect to the detected stone type. Children are in the high-risk group for stone recurrence (See chapter 4).

3.4.15.8 Summary of evidence and guidelines for the management of stones in children

Summary of evidence	LE
In children, the indications for SWL, URS and PNL are similar to those in adults.	1b
Children with renal stones of a diameter up to 20 mm (~300 mm^2) are ideal candidates for SWL.	1b
Ureteroscopy has become the treatment of choice for larger distal ureteral stones in children.	1a
In children, the indications for PNL are similar to those in adults.	1a

Recommendations	Strength rating
Offer children with single ureteral stones > 10 mm shock wave lithotripsy (SWL) if localisation is possible or ureteroscopy as first-line option.	Strong
Ureteroscopy is a feasible alternative for ureteral stones not amenable to SWL.	Strong
Offer children with renal stones with a diameter of up to 20 mm (~300 mm^2) SWL.	Strong
Offer children with renal pelvic or calyceal stones with a diameter > 20 mm (~300 mm^2) percutaneous nephrolithotomy.	Strong
Retrograde renal surgery is a feasible alternative for renal stones smaller than 20 mm in all locations.	Weak

3.5 Radiation exposure and protection during endourology

The diagnosis and treatment of nephrolithiasis is associated with high levels of ionising radiation exposure to patients [525, 526]. Currently, there are no studies estimating the lifetime radiation exposure of stone formers or the subsequent risk of malignancy development. The radiation exposure of endourologists has been extensively studied. Still, there are no studies assessing the risk of radiation induced malignancies in urologists or operating theatre staff members [527-529].

Current evidence from atomic bomb patients [530, 531], retrospective epidemiological data on medical exposure [532, 533] and modelling studies [534, 535] suggest an age and dose dependent risk of secondary malignancy from ionising radiation.

The International Commission on Radiological Protection (ICRP) recommends a maximum annual occupational exposure of 50mSv [536]. However, the risk of radiation induced malignancy follows a stochastic model having no known safe threshold of exposure. Taking this into consideration as well as the length of a urologists career the upper limit of 50mSv is still highly concerning.

Table 3.12 shows the EAU Urolithiasis guidelines panel recommended protection methods to reduce radiation exposure to patients, surgical, anaesthesiologic and nursing staff.

Table 3.12 Radiation protection measures

• Limit studies or intervention involving radiation exposure to those that are strictly medically necessary.
• Implement a patient electronic record of medical imaging.
• Make use of imaging studies with lower radiation doses (US, KUB, digital tomosynthesis, low-dose and ultra-low dose CT scan).
• Create and follow a precise radiation exposure protection protocol in your department.
• Act in accordance with the as low as reasonably achievable (ALARA) principle.
• Measure and report fluoroscopy time to the operative surgeon (use dosimeters and perform monthly calculations).

• Technical measures to reduce radiation exposure include: ■ Reducing fluoroscopy time; ■ Limiting time adjacent to patient; ■ Using low-dose radiation; ■ Irradiating only to observe motion; ■ Intra-operative use of pulsed fluoroscopy; ■ Reduced fluoroscopy pulse rate; ■ Collimated fields; ■ Avoid digital image acquisition and rely on last image hold and instant replay technology.
• Use radiation protection instruments (chest, pelvic and thyroid shields, lead or lead-free gloves, protective glasses, lead protection under the operating table between the X-ray source and the surgeon).
• The radiation protection instruments must be cared for appropriately as any damage decreases effectiveness and increases exposure risk. They should be monitored and measured regularly to ensure integrity.
• Proper surgeon and operating room setup should be observed (follow the inverse square law, use the X-ray source underneath the patient's body, decrease the X-ray source to patient distance, reduce magnification, avoid field overlap by not turning the C-arm in extreme angles, operate in the standing rather than the seated position).

Availability of fluoroscopy is mandatory for endourological procedures. There is an increasing interest on fluoroless and fluoroscopy-free operations in urology. Several RCTs have been published showing a good outcome in means of stone-free and complication rates [176, 289, 537-539]. These trials have been limited to non-complex cases and they were not sufficiently powered to show non-inferiority of fluoroscopy in PNL [289, 527] or superiority of US in URS [540, 541]

4. METABOLIC EVALUATION AND RECURRENCE PREVENTION

4.1 General metabolic considerations for patient work-up

4.1.1 ***Evaluation of patient risk***

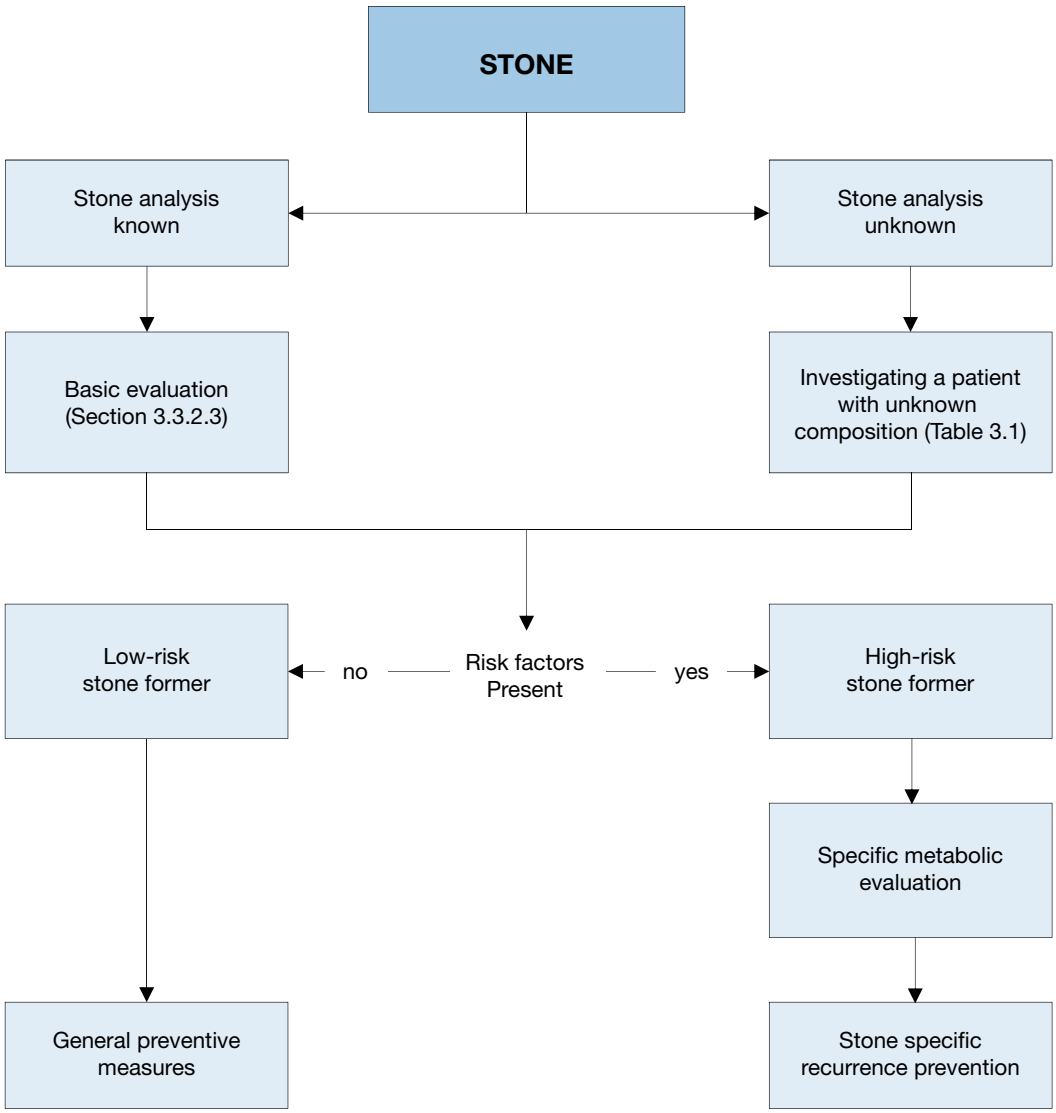
After stone passage, every patient should be assigned to a low- or high-risk group for stone formation (Figure 4.1). For correct classification, two items are mandatory:

- reliable stone analysis by infrared spectroscopy or X-ray diffraction;
- basic analysis (section 3.3.2).

Only high-risk stone formers require specific metabolic evaluation. Stone type is the deciding factor for further diagnostic tests. The different stone types include:

- calcium oxalate;
- calcium phosphate;
- uric acid;
- ammonium urate;
- struvite (and infection stones);
- cystine;
- xanthine;
- 2,8-Dihydroxyadenine;
- drug stones;
- stones of unknown composition.

Figure 4.1: Assignment of patients to low- or high-risk groups for stone formation



4.1.2 Urine sampling

Specific metabolic evaluation requires collection of two consecutive 24-hour urine samples [542, 543]. The collecting bottles should be prepared with 5% thymol in isopropanol or stored at < 8°C during collection to prevent the risk of spontaneous crystallisation in the urine. Pre-analytical errors can be minimised by carrying out urinalysis immediately after collection. Alternatively, boric acid (10 g powder per urine container) can also be used. The collecting method should be chosen in close cooperation with the laboratory. Urine pH should be assessed during collection of freshly voided urine at different times throughout the day using sensitive pH-dipsticks or a pH-meter [25, 544, 545].

Spot urine samples are an alternative method of sampling, particularly when 24-hour's urine collection is difficult, for example, in non-toilet trained children [546]. Spot urine studies normally link the excretion rates to creatinine [547], but these are of limited use because the results may vary with collection time and patients' sex, body weight and age.

4.1.3 Timing of specific metabolic work-up

For the initial specific metabolic work-up, the patient should stay on a self-determined diet under normal daily conditions and should ideally be stone free for at least twenty days [548]. Follow-up studies are necessary in patients taking medication for recurrence prevention [549]. The first follow-up 24-hour urine measurement is suggested eight to twelve weeks after starting pharmacological prevention of stone recurrence. This enables drug dosage to be adjusted if urinary risk factors have not normalised, with further 24-hour urine measurements, if necessary. Once urinary parameters have been normalised, it is sufficient to perform 24-hour urine evaluation every twelve months. On this issue the Panel realise that there is only very limited published evidence.

4.1.4 Reference ranges of laboratory values

Tables 4.1-4.4 provide the internationally accepted reference ranges for the different laboratory values in serum and urine.

Table 4.1: Normal laboratory values for blood parameters in adults [549, 550]

Blood parameter	Reference range	
Creatinine	20-100 µmol/L	
Sodium	135-145 mmol/L	
Potassium	3.5-5.5 mmol/L	
Calcium	2.0-2.5 mmol/L (total calcium)	
	1.12-1.32 mmol/L (ionised calcium)	
Uric acid	119-380 µmol/L	
Chloride	98-112 mmol/L	
Phosphate	0.81-1.29 mmol/L	
Blood gas analysis	pH	7.35-7.45
	pO_2	80-90 mmHg
	pCO_2	35-45 mmHg
	HCO_3	22-26 mmol/L
	BE	BE ± 2 mmol/L

BE = base excess (loss of buffer base to neutralise acid); HCO_3 = bicarbonate; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen.

4.1.5 Risk indices and additional diagnostic tools

Several risk indices have been developed to describe the crystallisation risk for calcium oxalate or calcium phosphate in urine [551-554]. However, clinical validation of these risk indices for recurrence prediction or therapy improvement is ongoing.

Table 4.2: Normal laboratory values for urinary parameters in adults

Urinary Parameters	Reference ranges and limits for medical attention
pH	Constantly > 5.8 (suspicious of renal tubular acidosis)
	Constantly > 7.0 (suspicious of infection)
	Constantly < 5.8 (suspicious of acidic arrest)
Specific weight	Specific weight > 1.010
Creatinine	7-13 mmol/day (females), 13-18 mmol/day (males)
Calcium	> 5.0 mmol/day (see Fig. 4.2)
	> 8.0 mmol/day (see Fig. 4.2)
Oxalate	> 0.5 mmol/day (suspicious of enteric hyperoxaluria)
	> 1.0 mmol/day (suspicious of primary hyperoxaluria)
Uric acid	> 4.0 mmol/day (females), 5 mmol/day (males)
Citrate	< 2.5 mmol/day
Magnesium	< 3.0 mmol/day
Inorganic phosphate	> 35 mmol/day
Ammonium	> 50 mmol/day
Cystine	> 0.8 mmol/day

Table 4.3: Normal values for spot urine samples: creatinine ratios (solute/creatinine) in children [555]

Parameter/Patient age	Ratio of solute to creatinine	Units
Calcium	**mol/mol**	**mg/mg**
< 12 months	< 2.0	0.81
1-3 years	< 1.5	0.53
1-5 years	< 1.1	0.39
5-7 years	< 0.8	0.28
> 7 years	< 0.6	0.21

Oxalate	**mol/mol**	**mg/mg**
0-6 months	< 325-360	288-260
7-24 months	< 132-174	110-139
2-5 years	< 98-101	80
5-14 years	< 70-82	60-65
> 16 years	< 40	32
Citrate	**mol/mol**	**g/g**
0-5 years	> 0.25	0.42
> 5 years	> 0.15	0.25
Magnesium*	**mol/mol**	**g/g**
All age groups	> 0.63	> 0.13
Uric acid		
> 2 years	< 0.56 mg/dL (33 µmol/L) per GFR (ratio x plasma creatinine)	

** There is low-level evidence regarding the importance of magnesium.*

Table 4.4: Solute excretion in 24-hour urine samples in children [556, 557]*****

Calcium/24 hour	**Citrate/24 hour**		**Cystine/24 hour**		**Oxalate/24 hour**		**Urate/24 hour**	
All age groups	Boys	Girls	< 10 years	> 10 years	All age groups	< 1 year	1-5 years	> 5 years
< 0.1 mmol/kg/24 h	> 1.9 mmol/1.73 m^2/24 h	> 1.6 mmol/1.73 m^2/24 h	< 55 µmol/1.73 m^2/24 h	< 200 µmol/1.73 m^2/24 h	< 0.5 mmol/1.73 m^2/24 h	< 70 µmol/kg/24 h	< 65 mµmol/kg/24 h	< 55 µmol/kg/24 h
< 4 mg/kg/24 h	> 365 mg/1.73 m^2/24 h	> 310 mg/1.73 m^2/24 h	< 13 mg/1.73 m^2/24 h	< 48 mg/1.73 m^2/24 h	< 45 mg /1.73 m^2/24 h	< 13 mg/kg/24 h	< 11 mg/kg/24 h	< 9.3 mg/kg/24 h

4.2 General considerations for recurrence prevention

All stone formers, independent of their individual risk, should follow the preventive measures in Table 4.5. The main focus is normalisation of dietary habits and lifestyle risks. Stone formers at high risk need specific prophylaxis for recurrence, which is usually pharmacological treatment based on stone analysis and urinary risk profile.

Table 4.5: General preventive measures

Fluid intake (drinking advice)	Fluid amount: 2.5-3.0 L/day
	Circadian drinking
	Neutral pH beverages
	Diuresis: 2.0-2.5 L/day
	Specific weight of urine: < 1,010 g/day
Nutritional advice for a balanced diet	Balanced diet*
	Rich in vegetables and fibre
	Normal calcium content: 1-1.2 g/day
	Limited NaCl content: 4-5 g/day
	Limited animal protein content: 0.8-1.0 g/kg/day
Lifestyle advice to normalise general risk factors	BMI: Retain a normal BMI level
	Adequate physical activity
	Balancing of excessive fluid loss

Caution: Protein requirements are age dependent; therefore, protein restriction in childhood should be handled carefully.

** Avoid excessive consumption of vitamin supplements.*

*4.2.1 **Fluid intake***

An inverse relationship between high fluid intake and stone formation has been repeatedly demonstrated [556-559]. The effect of fruit juices is mainly determined by the presence of citrate or bicarbonate [560]. If hydrogen ions are present, the net result is neutralisation. However, if potassium is present, both pH and citrate are increased [561, 562]. One large moderate quality RCT randomly assigned men with more than one past renal stone of any type and soft drink consumption of at least 160 mL/day to reduced soft drink intake or no treatment. Although the intervention significantly reduced the risk for symptomatic recurrent stones (RR: 0.83; CI: 0.71-0.98), the level of evidence for this outcome is low because results were from only one trial [563]. An

analysis on the three Channing's cohorts (194,095 participants) over a median follow-up of more than eight years has shown that consumption of sugar-sweetened soda and punch is associated with a higher risk of stone formation, whereas consumption of coffee, tea, beer, wine, and orange juice is associated with a lower risk [564].

*4.2.2 **Diet***

A common-sense approach to diet should be taken, that is, a mixed, balanced diet with contributions from all food groups, without any excesses [557, 565, 566].

Fruit, vegetables and fibre: Fruit and vegetable intake should be encouraged because of the beneficial effects of fibre, although the role of the latter in preventing stone recurrences is debatable [567-570]. The alkaline content of a vegetarian diet also increases urinary pH.

Oxalate: Excessive intake of oxalate-rich products should be limited or avoided to prevent high oxalate load [571], particularly in patients who have high oxalate excretion.

Vitamin C: Although vitamin C is a precursor of oxalate, its role as a risk factor in calcium oxalate stone formation remains controversial [572]. However, it seems wise to advise calcium oxalate stone formers to avoid excessive intake.

Animal protein: Animal protein should not be consumed in excess [573, 574] and limited to 0.8-1.0 g/kg body weight. Excessive consumption of animal protein has several effects that favour stone formation, including hypocitraturia, low urine pH, hyperoxaluria and hyperuricosuria.

Calcium intake: Calcium should not be restricted, unless there are strong reasons for doing so, due to the inverse relationship between dietary calcium and stone formation [568, 575]. The daily requirement for calcium is 1,000 to 1,200 mg [25]. Calcium supplements are not recommended except in enteric hyperoxaluria, when additional calcium should be taken with meals to bind intestinal oxalate [557, 571, 573, 576]. Older adults who do not have a history of renal stones but who take calcium supplements should ensure adequate fluid intake since it may prevent increases in urine calcium concentration, and thereby reduce or eliminate any increased risk of renal stones formation associated with calcium supplement use [577].

Sodium: Daily sodium (NaCl) intake should not exceed 3-5 g [25]. High intake adversely affects urine composition:

- calcium excretion is increased by reduced tubular re-absorption;
- urinary citrate is reduced due to loss of bicarbonate;
- increased risk of sodium urate crystal formation.

Calcium stone formation can be reduced by restricting sodium and animal protein [573, 574]. A positive correlation between sodium consumption and risk of first-time stone formation has been confirmed only in women [575]. There have been no prospective clinical trials on the role of sodium restriction as an independent variable in reducing the risk of stone formation.

Urate: Intake of purine-rich food should be restricted in patients with hyperuricosuric calcium oxalate [578, 579] and uric acid stones. Intake should not exceed 500 mg/day [25].

*4.2.3 **Lifestyle***

Lifestyle factors may influence the risk of stone formation, for example, obesity [580] and arterial hypertension [581, 582].

*4.2.4 **Summary of evidence and guideline for recurrence prevention***

Summary of evidence	**LE**
Increasing fluid intake reduces the risk of stone recurrence.	1a

Recommendation	**Strength rating**
Advise patients that a generous fluid intake is to be maintained, allowing for a 24-hour urine volume > 2.5 L.	Strong

4.3 Stone-specific metabolic evaluation and pharmacological recurrence prevention

*4.3.1 **Introduction***

Pharmacological treatment is necessary in patients at high risk for stone formation. The ideal drug should halt stone formation, have no side effects, and be easy to administer. Each of these aspects is important to achieve good compliance. Table 4.6 highlights the most important characteristics of commonly used medication.

Table 4.6: Pharmacological substances used for stone prevention - characteristics, specifics and dosage

Agent	Rationale	Dose	Specifics and side effects	Stone type	Ref
Alkaline citrates	Alkalinisation Hypocitraturia Inhibition of calcium oxalate crystallisation	5-12 g/d (14-36 mmol/d) Children: 0.1-0.15 g/kg/d	Daily dose for alkalinisation depends on urine pH.	Calcium oxalate Uric acid Cystine	[583-588]
Allopurinol	Hyperuricosuria Hyperuricaemia	100-300 mg/d Children: 1-3 mg/kg/d	100 mg in isolated hyperuricosuria. Renal insufficiency demands dose correction. Allergies from trivial to very severe forms, xanthine stone formation.	Calcium oxalate Uric acid Ammonium urate 2,8-Dihydroxyadenine	[577, 589-592]
Calcium	Enteric hyperoxaluria	Up to 2,000 mg/d depending on oxalate excretion	Intake 30 min before meals.	Calcium oxalate	[573, 575, 576]
Captopril	Cystinuria Active decrease of urinary cystine levels	75-150 mg	Second-line option due to significant side effects of tiopronin.	Cystine	[593, 594]
Febuxostat	Hyperuricosuria Hyperuricaemia	80-120 mg/d	Acute gout contraindicated, pregnancy, xanthine stone formation.	Calcium oxalate Uric acid	[595, 596]
L-Methionine	Acidification	600-1,500 mg/d	Hypercalciuria, bone demineralisation, systemic acidosis. No long-term therapy.	Infection stones Ammonium urate Calcium phosphate	[583, 597]
Magnesium	Isolated hypomagnesiuria Enteric hyperoxaluria	200-400 mg/d Children: 6 mg/kg/d	Renal insufficiency demands dose correction. Diarrhoea, chronic alkali losses, hypocitraturia.	Calcium oxalate	[598, 599] (Low level of evidence)
Sodium bicarbonate	Alkalinisation Hypocitraturia	4.5 g/d	N/A	Calcium oxalate Uric acid, Cystine	[600]
Pyridoxine	Primary hyperoxaluria	Initial dose 5 mg/kg/d Max. 20 mg/kg/d	Polyneuropathia	Calcium oxalate	[601]
Thiazide (Hydrochlorothiazide*)	Hypercalciuria	25-50 mg/d Children: 0.5-1 mg/kg/d	Risk for hypotonic blood pressure, diabetes, hyperuricaemia, hypokalaemia, followed by intracellular acidosis and hypocitraturia.	Calcium oxalate Calcium phosphate	[579, 581-609]

Tiopronin	Cystinuria Active decrease of urinary cystine levels	Initial dose 800 mg/d Avg. 2,000 mg/d** Children: Initial dose in patients > 20kg is 15 mg/kg/day. Avoid dosages > 50mg/kg/day	Risk for tachyphylaxis and proteinuria.	Cystine	[610-613]

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk of developing a non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [614, 615].*

*** No information is available on maximum dose and patients may be initiated on a very low dose if they have had previously had reactions to tiopronin or penicillamine. For all patients, dosage should be titrated according to frequency of stone episodes, side effects and renal function under expert supervision with close monitoring.*

4.4 Calcium oxalate stones

The criteria for identification of calcium oxalate stone formers with high recurrence risk are listed in section 3.1.3.

*4.4.1 **Diagnosis***

Blood analysis requires measurement of creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate, uric acid; and, in the case of increased calcium levels, parathyroid hormone (PTH) and vitamin D. Urinalysis requires measurement of urine volume, urine pH profile, specific weight, calcium, oxalate, uric acid, citrate, sodium and magnesium. Figure 4.2 summarises the diagnostic steps for calcium oxalate stones.

*4.4.2 **Interpretation of results and aetiology***

The most common metabolic abnormalities associated with calcium stone formation are hypercalciuria, which affects 30-60% of adult stone formers, and hyperoxaluria (26-67%), followed by hyperuricosuria (15-46%), hypomagnesuria (7-23%), and hypocitraturia (5-29%). However, ranges tend to differ based on ethnicity [616].

- Elevated levels of ionised calcium in serum (or total calcium and albumin) require assessment of intact PTH to confirm or exclude suspected hyperparathyroidism (HPT).
- “Acidic arrest” (circadian urine pH constantly < 5.8) may promote co-crystallisation of uric acid and calcium oxalate.
- Similarly, increased uric acid excretion (> 4 mmol/day in adults or > 12 mg/kg/day in children) can act as a promoter.
- Urine pH levels constantly > 5.8 in the day profile may indicate RTA, provided UTI has been excluded. An ammonium chloride loading test confirms RTA and identifies RTA subtype (section 4.6.5).
- Hypercalciuria may be associated with normocalcemia (idiopathic hypercalciuria, or granulomatous diseases) or hypercalcaemia (hyperparathyroidism, granulomatous diseases, vitamin D excess, or malignancy).
- Hypocitraturia (male < 1.7 mmol/day, female < 1.9 mmol/day) may be idiopathic or secondary to metabolic acidosis or hypokalaemia.
- Oxalate excretion > 0.5 mmol/day in adults (> 0.37 mmol/1.73 m^2/day in children) confirms hyperoxaluria.
    - o primary hyperoxaluria (oxalate excretion mostly > 1 mmol/day), appears in three genetically determined forms;
    - o secondary hyperoxaluria (oxalate excretion > 0.5 mmol/day, usually < 1 mmol/day), occurs due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake;
    - o mild hyperoxaluria (oxalate excretion 0.45-0.85 mmol/day), commonly found in idiopathic calcium oxalate stone formers.
- Hypomagnesuria (< 3.0 mmol/day) may be related to poor dietary intake or to reduced intestinal absorption (chronic diarrhoea).

Figure 4.2: Diagnostic algorithm for calcium oxalate stones

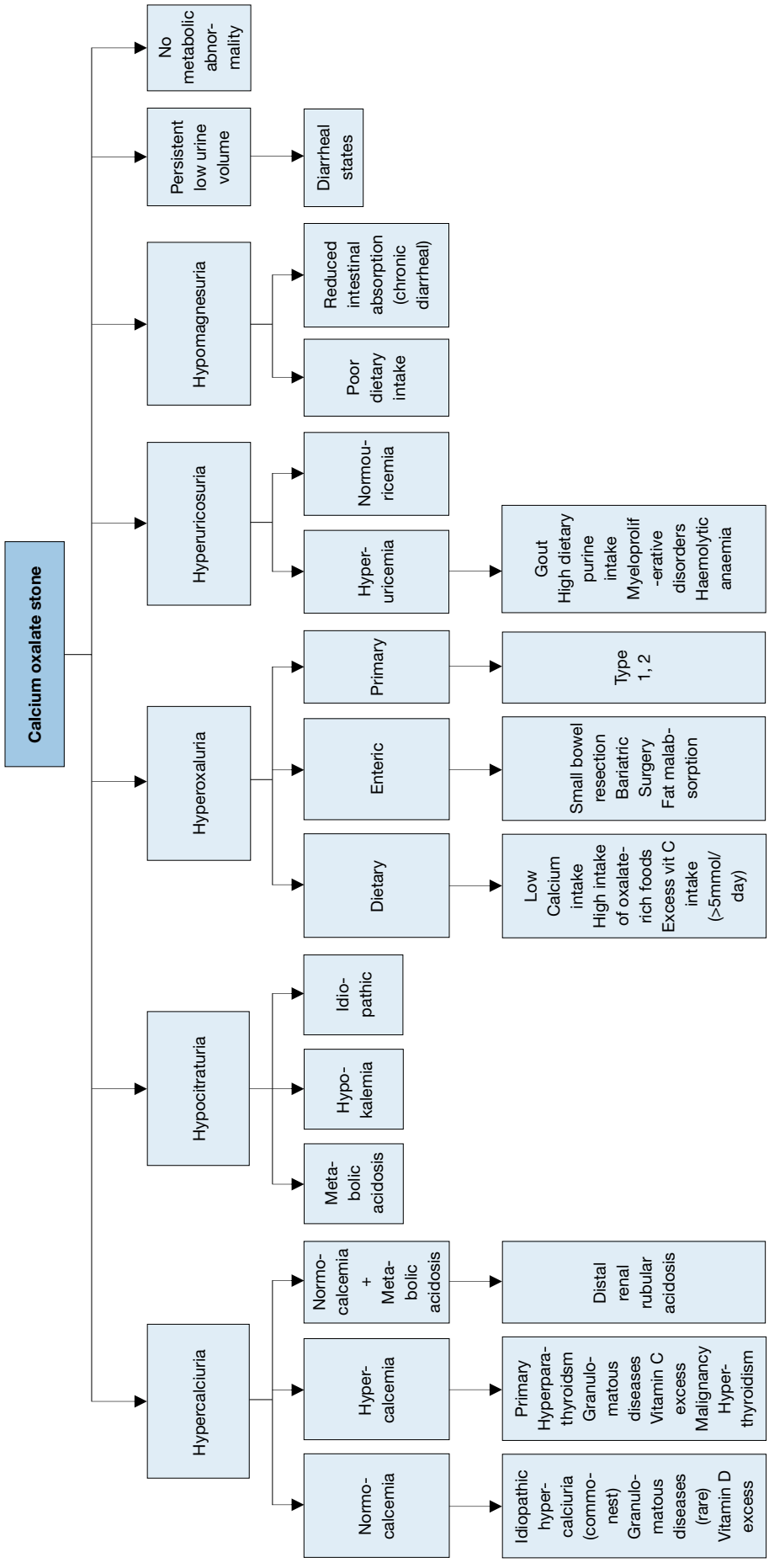
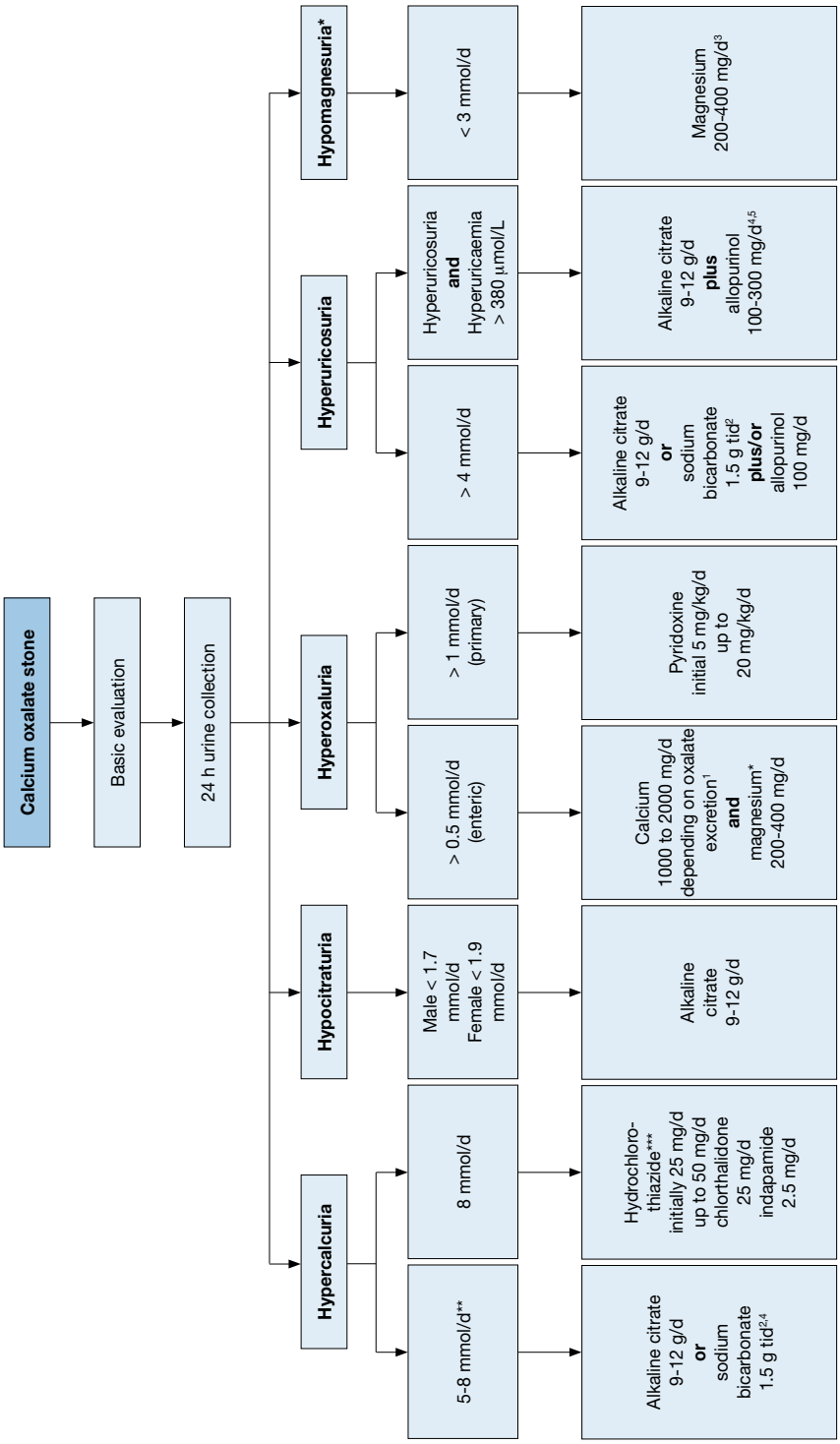


Figure 4.3: Therapeutic algorithm for calcium oxalate stones



[1] *Be aware of excess calcium excretion.*

[2] *tid = three times/day (24h).*

[3] *No magnesium therapy for patients with renal insufficiency.*

[4] *There is no evidence that combination therapy (thiazide + citrate) or (thiazide + allopurinol) is superior to thiazide therapy alone [584, 617].*

[5] *Febuxostat 80 mg/day.*

** low evidence (see text)*

***Calciuria is a continuous variable and treatment may be adjusted to clinical need even when below the threshold indicated.*

****Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk for developing non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [614, 615].*

4.4.3 Specific treatment

General preventive measures are recommended for fluid intake and diet. Hyperoxaluric stone formers should consume foods with low oxalate content, whereas hyperuricosuric stone formers benefit from daily dietary reduction of purine. Figure 4.3 summarises the pharmacological treatment of calcium oxalate stones [557, 562, 583-586, 589, 590, 592, 595, 598-600, 602-609, 616, 618-620]. There is only low-level evidence for the efficacy of preventing stone recurrence based on pre-treatment stone composition examination and biochemistry measures, or on-treatment biochemistry measures [557].

4.4.4 Summary of evidence and guidelines for pharmacological treatments for patients with specific abnormalities in urine composition (based on 24-hour urine samples)

Summary of evidence	LE
Thiazide or alkaline citrates or both can reduce stone formation.	1a
Oxalate restriction is beneficial if hyperoxaluria is present.	2b
Alkaline citrates can reduce stone formation in enteric hyperoxaluria.	4
Calcium supplement can reduce stone formation in enteric hyperoxaluria.	2
A diet low in fat and oxalate can be beneficial in reducing stone formation.	3
Alkaline citrates and sodium bicarbonate can be used if hypocitraturia is present.	1b
Allopurinol is first-line treatment of hyperuricosuria.	1a
Febuxostat is second-line treatment of hyperuricosuria.	1b
Avoid excessive intake of animal protein in hyperuricosuria.	1b
Restricted intake of salt is beneficial if there is high urinary sodium excretion.	1b

Recommendations	Strength rating
Prescribe thiazide or alkaline citrates or both in case of hypercalciuria*.	Strong
Advise oxalate restriction if hyperoxaluria is present.	Weak
Offer alkaline citrates in enteric hyperoxaluria.	Weak
Offer calcium supplement in enteric hyperoxaluria.	Weak
Advise reduced dietary fat and oxalate in enteric hyperoxaluria.	Weak
Prescribe alkaline citrates and sodium bicarbonate in case of hypocitraturia.	Strong
Prescribe allopurinol in case of hyperuricosuria.	Strong
Offer febuxostat as second-line treatment of hyperuricosuria.	Strong
Avoid excessive intake of animal protein in hyperuricosuria.	Strong
Advise restricted intake of salt if there is high urinary sodium excretion.	Strong

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk of developing a non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [614, 615].*

4.5 Calcium phosphate stones [557, 583, 592, 602, 603, 607, 621]

Some calcium phosphate stone formers are at high risk of recurrence. Further information on identifying high-risk patients is provided in section 3.1.3.

Calcium phosphate mainly appears in two completely different minerals: carbonate apatite and brushite. Carbonate apatite crystallisation occurs at a pH > 6.8 and may be associated with infection. Brushite crystallises at an optimum pH of 6.5-6.8 at high urinary concentrations of calcium (> 8 mmol/day) and phosphate (> 35 mmol/day). Its occurrence is not related to UTI. Possible causes of calcium phosphate stones include HPT, RTA and UTI; each of which requires different therapy.

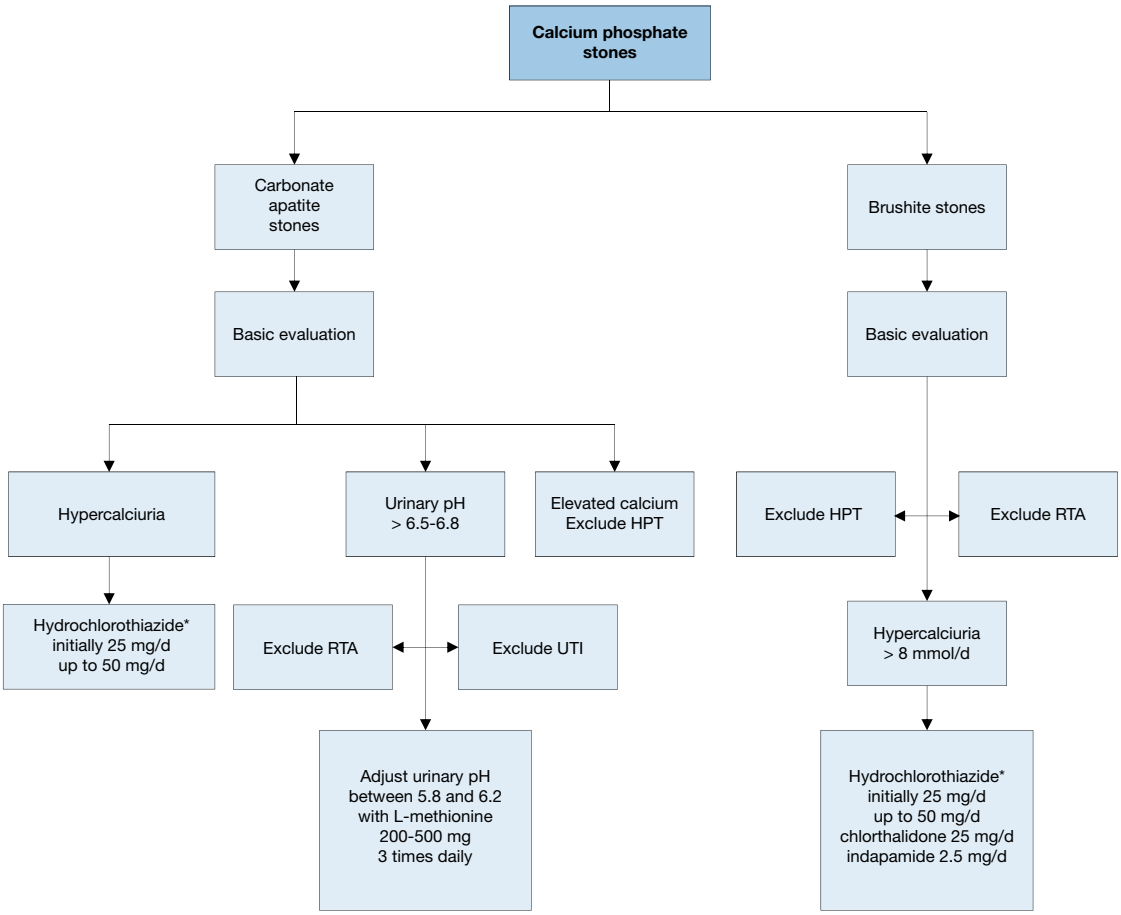
4.5.1 Diagnosis

Diagnosis requires blood analysis for: creatinine, sodium, potassium, chloride, ionised calcium (or total calcium + albumin), phosphate, and PTH (in the case of increased calcium levels). Urinalysis includes measurement of: volume, urine pH profile, specific weight, calcium, phosphate and citrate.

4.5.2 Interpretation of results and aetiology

General preventative measures are recommended for fluid intake and diet. The diagnostic and therapeutic algorithm for calcium phosphate stones is shown in Figure 4.4.

Figure 4.4: Diagnostic and therapeutic algorithm for calcium phosphate stones


Calcium phosphate stones
Carbonate apatite stones
Brushite stones
Basic evaluation
Basic evaluation
Hypercalciuria
Urinary pH > 6.5-6.8
Elevated calcium Exclude HPT
Exclude HPT
Exclude RTA
Hydrochlorothiazide* initially 25 mg/d up to 50 mg/d
Exclude RTA
Exclude UTI
Hypercalciuria > 8 mmol/d
Adjust urinary pH between 5.8 and 6.2 with L-methionine 200-500 mg 3 times daily
Hydrochlorothiazide* initially 25 mg/d up to 50 mg/d chlorthalidone 25 mg/d indapamide 2.5 mg/d

HPT = hyperparathyroidism; RTA = renal tubular acidosis; UTI = urinary tract infection.

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk for developing non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [614, 615].*

*4.5.3 **Pharmacological therapy** [557, 583, 592, 602, 603, 607, 621]*

Hyperparathyroidism and RTA are common causes of calcium phosphate stone formation. Most patients with primary HPT require surgery. Renal tubular acidosis can be corrected pharmacologically including with bicarbonate or alkaline citrate therapy. If primary HPT and RTA have been excluded, pharmacotherapy for calcium phosphate calculi depends on effective reduction of urinary calcium levels using thiazides. For infection-associated calcium phosphate stones, it is important to consider the guidance given for infection stones.

*4.5.4 **Summary of evidence and guidelines for the management of calcium phosphate stones***

Summary of evidence	LE
Thiazide is beneficial in case of hypercalciuria.	1a

Recommendation	Strength rating
Prescribe thiazide in case of hypercalciuria.	Strong

4.6 Disorders and diseases related to calcium stones

*4.6.1 **Hyperparathyroidism** [622-624]*

Primary HPT is responsible for an estimated 5% of all calcium stone formation. Renal stones occur in approximately 20% of patients with primary HPT. Elevated levels of PTH significantly increase calcium turnover, leading to hypercalcaemia and hypercalciuria and bone disease. Serum calcium may be mildly elevated and serum PTH may be within the upper normal limits and, therefore, repeated measurements may be needed;

preferably with the patient fasting. Stones of HPT patients may contain both calcium oxalate and calcium phosphate. Nephrocalcinosis and CKD may also occur.

If HPT is suspected, neck exploration should be performed to confirm the diagnosis. Primary HPT can only be cured by surgery.

*4.6.2 **Granulomatous diseases** [625]*

Granulomatous diseases, such as sarcoidosis, may be complicated by hypercalcaemia and hypercalciuria secondary to increased calcitriol production. The latter is independent of PTH control, leading to increased calcium absorption in the gastrointestinal tract and suppression of PTH. Treatment focuses on the activity of the granulomatous diseases and may require steroids, hydroxychloroquine or ketoconazole. Treatment should be reserved for a specialist.

*4.6.3 **Primary hyperoxaluria** [601]*

Patients with primary hyperoxaluria (PH) should be referred to specialised centres, as successful management requires an experienced interdisciplinary team. The main therapeutic aim is to reduce endogenous oxalate production, which is increased in patients with PH. In approximately one-third of patients with PH type I, pyridoxine therapy normalises or significantly reduces urinary oxalate excretion. The goal of adequate urine dilution is achieved by adjusting fluid intake to 3.5-4.0 L/day in adults (children 1.5 L/m^2 body surface area) and following a circadian drinking regimen.

Therapeutic options for preventing calcium oxalate crystallisation include hyperdiuresis, alkaline citrates, magnesium and Lumasiran, an RNAi agent, a new treatment for reducing the synthesis of oxalate of PH type 1 [626]. However, in end-stage renal failure, PH requires simultaneous liver-kidney transplantation.

Treatment regimens are:

- pyridoxine in PH type I: 5-20 mg/kg/day according to urinary oxalate excretion and patient tolerance;
- alkaline citrate: 9-12 g/day in adults, 0.1-0.15 mq/kg/day in children;
- magnesium: 200-400 mg/day (no magnesium in the case of renal insufficiency);
- Lumasiran: Subcutaneous injection with dose and timing adjusted according to body weight and duration of treatment.

4.6.3.1 Summary of evidence and guideline for the management of primary hyperoxaluria

Summary of evidence	**LE**
Pyridoxine can reduce the urinary oxalate excretion in primary hyperoxaluria.	3

Recommendation	**Strength rating**
Prescribe pyridoxine for primary hyperoxaluria.	Strong

*4.6.4 **Enteric hyperoxaluria** [571, 576, 627-629]*

Enteric hyperoxaluria is a particularly problematic condition in patients with intestinal malabsorption of fat. This abnormality is associated with a high risk of stone formation and is seen after intestinal resection and malabsorptive bariatric surgery, as well as in Crohn's disease and pancreas insufficiency. In addition to hyperoxaluria, these patients usually present with hypocitraturia due to loss of alkali. Urine pH is usually low, as are urinary calcium and urine volume. All these abnormalities contribute to high levels of supersaturation with calcium oxalate, crystalluria, stone formation, and less frequently to nephrocalcinosis and CKD. Specific preventive measures are:

- restricted intake of oxalate-rich foods [571];
- restricted fat intake [571];
- calcium supplementation at meal times to enable calcium oxalate complex formation in the intestine [576, 627-629];
- sufficient fluid intake to balance intestinal loss of water caused by diarrhoea;
- alkaline citrates to raise urinary pH and citrate.

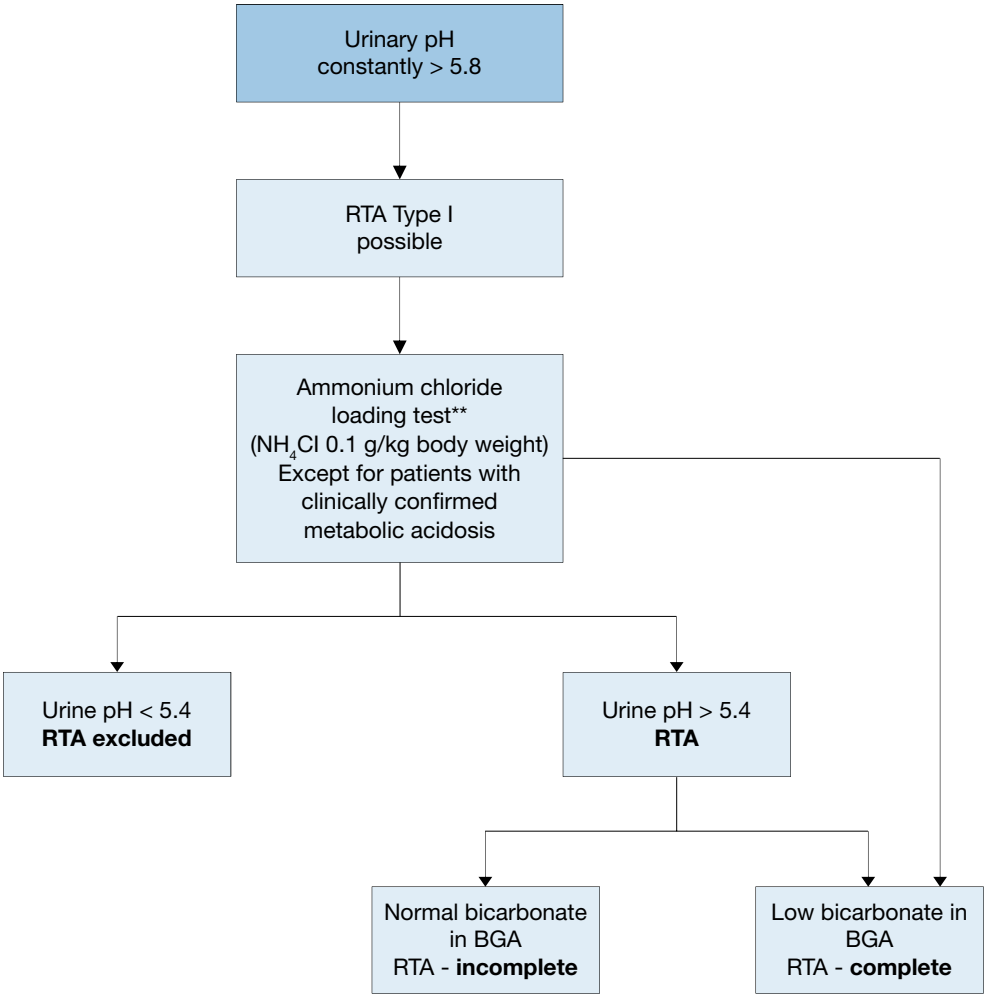
Summary of evidence	**LE**
Alkaline citrates can be beneficial to replace citrate loss and raise urine pH.	3
Calcium supplements with meals enable calcium oxalate complex formation in the intestine.	2
Reduction in dietary fat and oxalate can be beneficial in intestinal malabsorption.	3

Recommendations	Strength rating
Prescribe alkaline citrates for enteric hyperoxaluria.	Weak
Advise patients to take calcium supplements with meals.	Weak
Advise patients to follow a diet with a low fat and oxalate content.	Weak

4.6.5 ***Renal tubular acidosis*** *[557, 592, 630, 631]*

Renal tubular acidosis is caused by severe impairment of proton or bicarbonate handling along the nephron. Kidney stone formation most probably occurs in patients with distal RTA type I. Figure 4.5 outlines the diagnosis of RTA. Table 4.7 shows acquired and inherited causes of RTA.

Figure 4.5: Diagnosis of renal tubular acidosis



BGA = blood gas analysis; RTA = renal tubular acidosis.

*** An alternative ammonium chloride loading test using NH4Cl load with 0.05 g/kg body weight over three days might provide similar results and may be better tolerated by the patient. A second alternative in these cases could be the furosemide/fludrocortisone acidification test [632].*

Renal tubular acidosis can be acquired or inherited. Reasons for acquired RTA can be chronic obstructive uropathy, recurrent pyelonephritis, acute tubular necrosis, renal transplantation, analgesic nephropathy, sarcoidosis, Sjögren syndrome and other autoimmune diseases, medullary sponge kidney, liver cirrhosis, sickle cell anaemia, idiopathic hypercalciuria, and primary parathyroidism; it may also be drug-induced (e.g., amphotericin B, foscarnet, lithium, zonisamide).

Table 4.7: Inherited causes of renal tubular acidosis

Type - inheritance	Gene/gene product/function	Phenotype
Autosomal dominant	SLC4A1/AE1/Cl-bicarbonate exchanger	Hypercalciuria, hypokalaemia, rickets/osteomalacia
Autosomal recessive with hearing loss	ATP6V1B1/B1 sub-unit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets/osteomalacia
Autosomal recessive	ATP6V0A4/A4 sub-unit of vacuolar H-ATPase/proton secretion	Hypercalciuria, hypokalaemia, rickets/osteomalacia

More rarely biallelic causative variants in FOXI1 and WDR72 genes have also been identified. The main therapeutic aim of RTA treatment is restoring a normal acid-base equilibrium. Despite the alkaline pH of urine in RTA, alkalinisation using alkaline citrates or sodium bicarbonate is important for normalising the metabolic changes (intracellular acidosis) responsible for stone formation (Table 4.8) and bone demineralisation. The alkali load reduces tubular re-absorption of citrate, which in turn normalises citrate excretion. Therapeutic success can be monitored by venous blood gas analysis (base excess: ± 2.0 mmol/L) in complete RTA. If excessive calcium excretion (> 8 mmol/day) persists after re-establishing acid-base equilibrium, thiazides may lower urinary calcium excretion.

Table 4.8: Pharmacological treatment of renal tubular acidosis

Biochemical risk factor	Indication for pharmacological therapy	Medication
Hypercalciuria	Calcium excretion > 8 mmol/day	Hydrochlorothiazide*, - in adults: 25 mg/day initially, up to 50 mg/day - in children: 0.5-1 mg/kg/day Alternatives in adults: Chlorthalidone 25 mg/day Indapamide 2.5 mg/day
Inadequate urine pH	Citrate excretion < 320 mg/day	Alkaline citrate, 9-12 g/day divided in three doses ***OR*** Sodium bicarbonate, 1.5 g, three times daily

** Patients on hydrochlorothiazides should be advised to get their skin checked on a regular basis as they have a higher risk of developing non-melanoma skin cancer (NMSC). In patients with history of NMSC the indication for the intake of hydrochlorothiazides should be thoroughly reviewed [614, 615].*

4.6.5.1 Summary of evidence and guidelines for the management of tubular acidosis

Summary of evidence	LE
Alkaline citrates can be beneficial in distal renal tubular acidosis to correct the intracellular acidosis.	2b
Thiazide and alkaline citrates are beneficial for hypercalciuria.	1a

Recommendations	Strength rating
Prescribe alkaline citrates for distal renal tubular acidosis.	Strong
Prescribe thiazide and alkaline citrates for hypercalciuria.	Strong

*4.6.6 **Nephrocalcinosis** [633]*

Nephrocalcinosis (NC) refers to increased calcium crystal deposition within the renal cortex or medulla and occurs alone or in combination with renal stones. There are various metabolic causes. The main causes are: HPT, primary and enteric hyperoxalurias, genetic and acquired RTA, medullary sponge kidney, vitamin D metabolic disorders, sarcoidosis, idiopathic hypercalciuria and hypocitraturia, and genetic disorders, including Dent's disease, Bartter's syndrome. The many causes of NC mean there is no single standard therapy. Therapeutic attention must focus on the underlying metabolic or genetic disease, on the frequent association with CKD while minimising the biochemical risk factors.

4.6.6.1 Diagnosis

Diagnosis requires the following blood analysis: PTH (in the case of increased calcium levels), vitamin D and metabolites, vitamin A, sodium, potassium, magnesium, chloride, and bicarbonate. Urinalysis should investigate urine pH profile at different times of the day [634], daily urine volume, specific weight of urine, and levels of calcium, oxalate, phosphate, uric acid, magnesium, and citrate.

4.7 Uric acid and ammonium urate stones

All uric acid and ammonium urate stone formers are considered to be at high risk of recurrence [25]. Uric acid nephrolithiasis is responsible for approximately 10% of renal stones [635] and associated with hyperuricosuria or low urinary pH. Hyperuricosuria may be a result of dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, chemotherapy drugs, gout or catabolism [636]. Low urinary pH may be caused by decreased urinary ammonium excretion (insulin resistance or gout), increased endogenous acid production (insulin resistance, metabolic syndrome, or exercise-induced lactic acidosis), increased acid intake (high animal protein intake), or increased base loss (diarrhoea) [636].

Ammonium urate stones are extremely rare, comprising < 1% of all types of urinary stones. They are associated with UTI, malabsorption (inflammatory bowel disease and ileostomy diversion or laxative abuse), phosphate deficiency, hypokalemia and malnutrition. Suggestions on uric acid and ammonium urate nephrolithiasis are based on level 3 and 4 evidence. Chronic kidney disease is frequently observed.

*4.7.1 **Diagnosis***

Figure 4.6 shows the diagnostic algorithm for uric acid stones and figure 4.7 shows the therapeutic algorithm for uric acid and ammonium urate stones. Blood analysis requires measurement of creatinine, potassium, and uric acid levels. Urinalysis requires measurement of urine volume, urine pH profile, specific weight of urine, and uric acid level. Urine culture is needed in the case of ammonium urate stones.

*4.7.2 **Interpretation of results***

Uric acid and ammonium urate stones form under completely different biochemical conditions. Acidic arrest (circadian urine pH constantly < 5.8) promotes uric acid crystallisation.

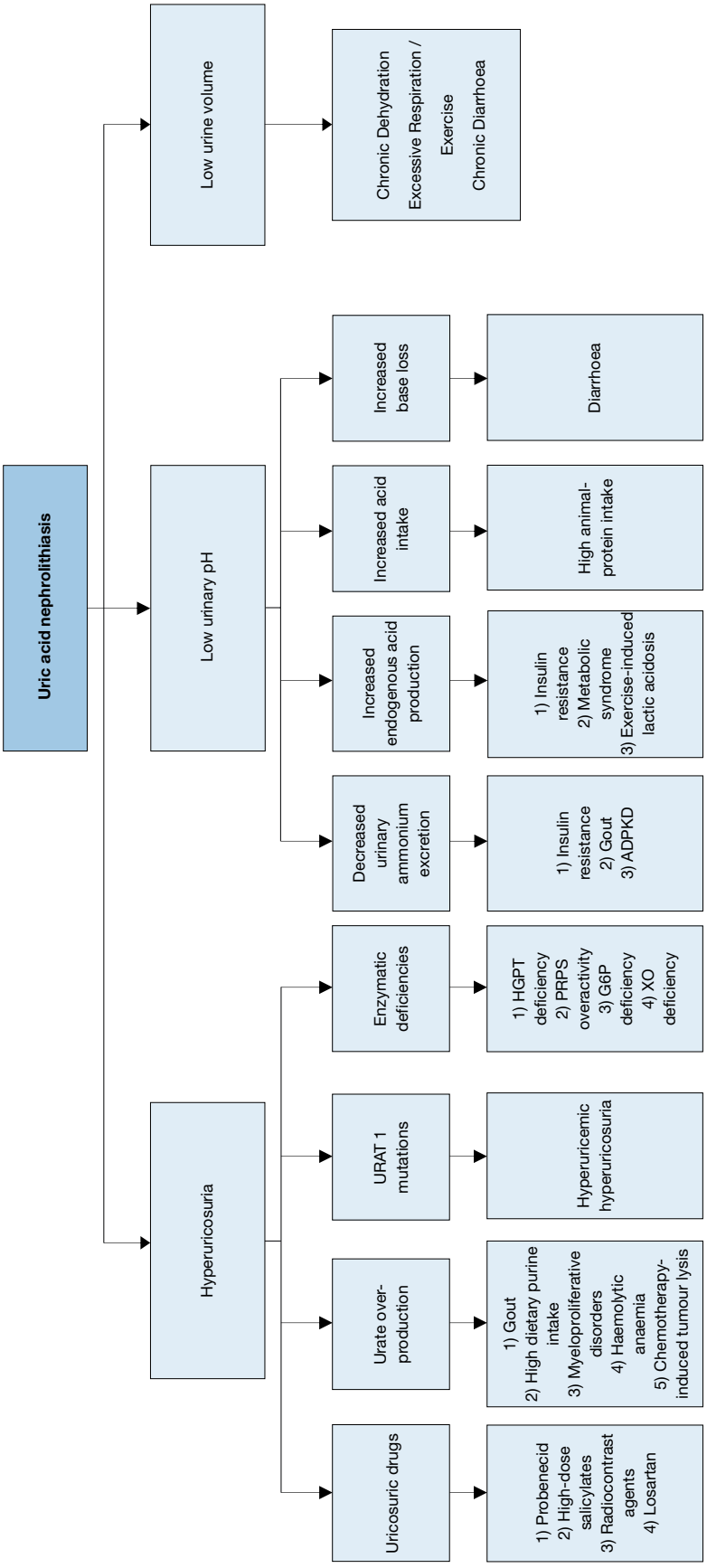
Hyperuricosuria is defined as uric acid excretion > 4 mmol/day in adults or > 0.12 mmol/kg/day in children. Hyperuricaemia may be present, but there is only weak evidence for its association with stone formation [637].

Hyperuricosuric calcium oxalate stone formation can be distinguished from uric acid stone formation by urinary pH, which is usually > 5.5 in calcium oxalate stone formation and < 5.5 in uric acid stone formation and occasional absence of hyperuricosuria in patients with pure uric acid stones [638, 639]. Ammonium urate crystals form in urine at pH > 6.5, high uric acid concentration when ammonium is present [640, 641].

*4.7.3 **Specific treatment***

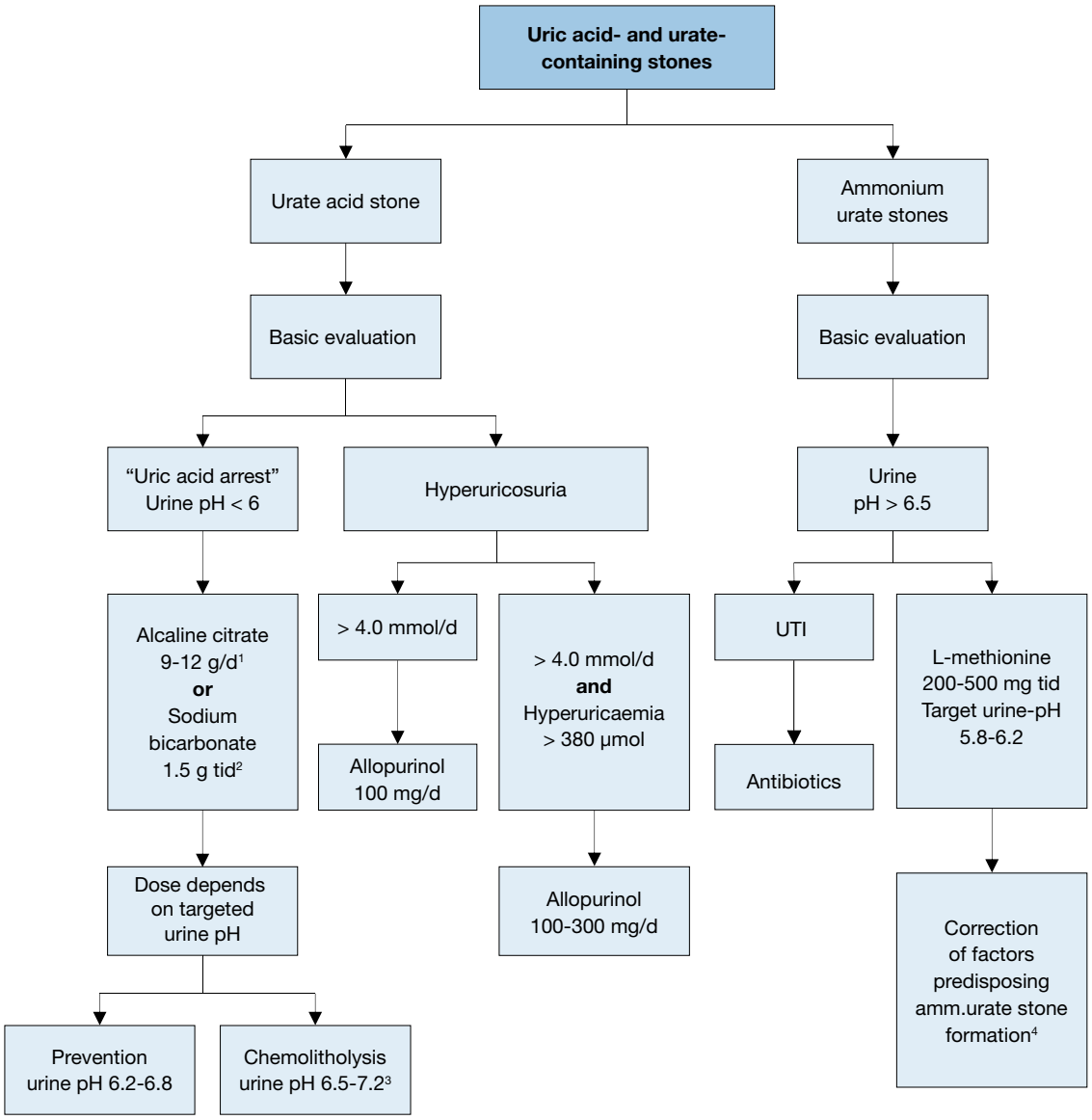
General preventive measures are recommended for fluid intake and diet. Hyperuricosuric stone formers benefit from purine reduction in their daily diet. Figure 4.6 describes pharmacological treatment [25, 547, 635, 638-647]. For uric acid stones, allopurinol may change the stone composition distribution in patients with gout to a pattern similar to that in stone formers without gout [648].

Figure 4.6: Diagnostic algorithm for uric acid stones



ADPKD = autosomal dominant polycystic kidney disease; G6P = glucose-6 phosphate dehydrogenase; HGPT = hypoxanthine guanine phosphorybosyl transferase; PRPS = phosphoribosyl-pyrophosphate synthetase superactivity; XO = xanthine oxidase.

Figure 4.7: Therapeutic algorithm for uric acid- and ammonium-urate stones


Uric acid- and urate-containing stones
Urate acid stone
Ammonium urate stones
Basic evaluation
Basic evaluation
"Uric acid arrest" Urine pH < 6
Hyperuricosuria
Urine pH > 6.5
Alcaline citrate 9-12 g/d[1] or Sodium bicarbonate 1.5 g tid[2]
> 4.0 mmol/d
> 4.0 mmol/d and Hyperuricaemia > 380 µmol
UTI
L-methionine 200-500 mg tid Target urine-pH 5.8-6.2
Allopurinol 100 mg/d
Antibiotics
Dose depends on targeted urine pH
Allopurinol 100-300 mg/d
Correction of factors predisposing amm.urate stone formation[4]
Prevention urine pH 6.2-6.8
Chemolitholysis urine pH 6.5-7.2[3]

[1] d: day.
[2] tid: three times a day.
[3] A higher pH may lead to calcium phosphate stone formation.
[4] In patients with high uric acid excretion, allopurinol may be helpful.

4.7.4 Summary of evidence and guidelines for the management of uric acid- and ammonium urate stones

Summary of evidence	LE
Alkaline citrates can be beneficial to alkalinise the urine in uric acid stone formers.	3
Allopurinol can be beneficial in hyperuricosuric urate stone formers.	1b

Recommendations	Strength rating
Prescribe alkaline citrates to alkalinise the urine in uric acid stone formers.	Strong
Prescribe allopurinol in hyperuricosuric urate stone formers.	Strong

4.8 Struvite and infection stones

All infection-stone formers are deemed at high risk of recurrence. Struvite stones represent 2-15% of the stones sent for analysis. Stones that contain struvite may originate *de novo* or grow on pre-existing stones, which are infected with urea-splitting bacteria [649]. There are several factors predisposing patients to struvite stone formation (Table 4.9) [650].

*4.8.1 **Diagnosis***

Blood analysis requires measurement of creatinine, and urinalysis requires repeat urine pH measurements and urine culture.

*4.8.2 **Interpretation***

Infection stones contain the following minerals: struvite and/or carbonate apatite and/or ammonium urate. Urine culture typically provides evidence for urease-producing bacteria, which increase ammonia ions and develop alkaline urine (Table 4.10). Carbonate apatite starts to crystallise at a urine pH level of 6.8. Struvite only precipitates at pH > 7.2 [651, 652]. *Proteus mirabilis* accounts for more than half of all urease-positive UTIs [653, 654].

*4.8.3 **Specific treatment***

General preventive measures are recommended for fluid intake and diet. Specific measures include complete surgical stone removal [650], short- or long-term antibiotic treatment [655], urinary acidification using methionine [597] or ammonium chloride [656], and advice to restrict intake of urease [657, 658]. For severe infections, acetohydroxamic acid may be an option [657, 658] (Figure 4.8); however, it is not licensed/available in all European countries.

Eradication of infection after complete stone removal is desirable. The evidence regarding the duration of post-operative antibiotic administration is inconclusive.

Summary of evidence	LE
Removing the stone material as completely as possible with surgery can reduce ongoing infection.	3
Antibiotics are beneficial after complete stone removal.	3
Ammonium chloride, 1 g, two or three times daily, can ensure urinary acidification to prevent recurrent infection.	3
Methionine, 200-500 mg, one to three times daily, can be used as an alternative to ammonium chloride, to ensure urinary acidification.	3
Urease inhibitors in case of severe infection are occasionally used (if licensed).	1b

Recommendations	Strength rating
Surgically remove the stone material as completely as possible.	Strong
Prescribe antibiotics in case of persistent bacteriuria.	Strong
Prescribe ammonium chloride, 1 g, two or three times daily to ensure urinary acidification.	Weak
Prescribe methionine, 200-500 mg, one to three times daily, as an alternative, to ensure urinary acidification.	Weak

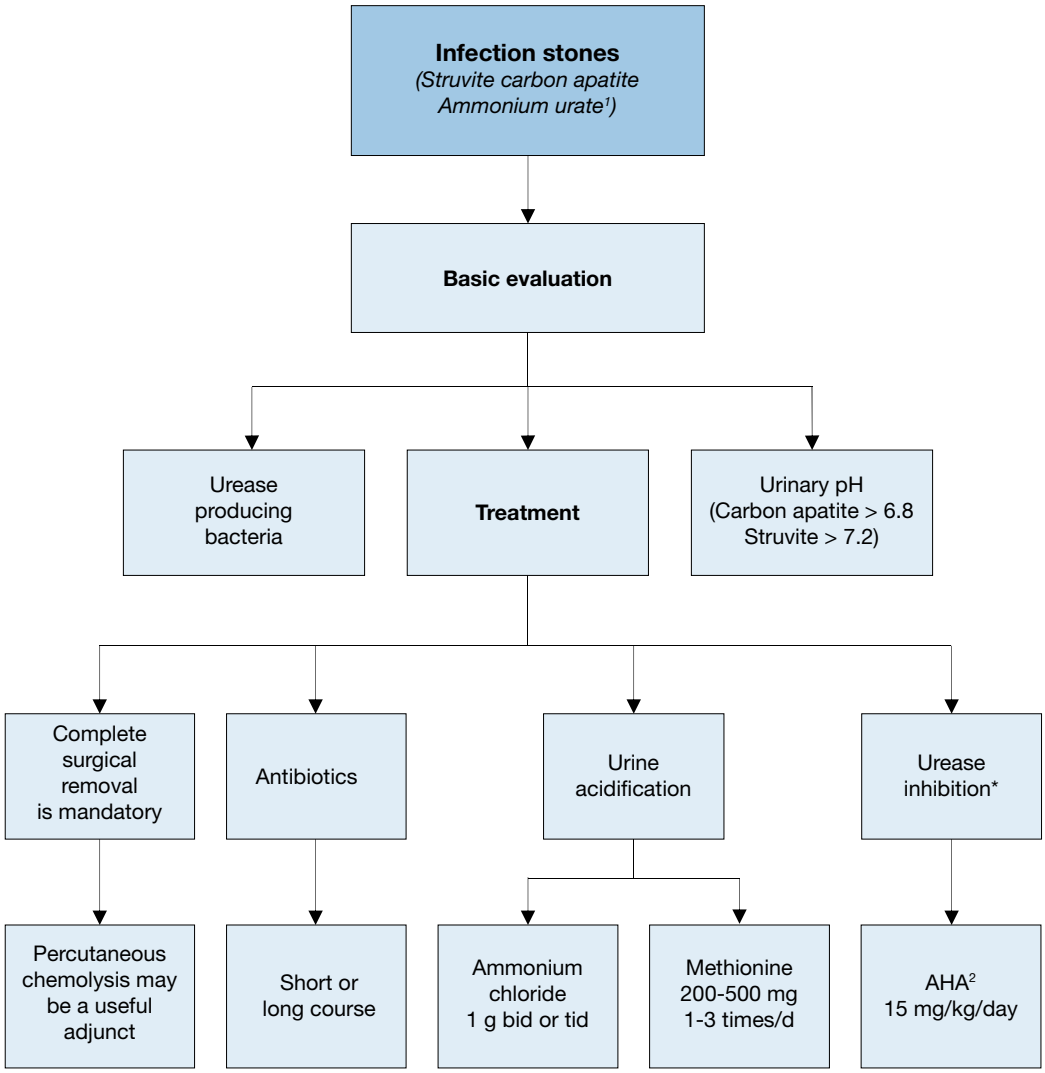
Table 4.9: Factors predisposing to struvite stone formation

• Neurogenic bladder • Spinal cord injury/paralysis • Continent urinary diversion • Ileal conduit • Foreign body • Stone disease • Indwelling urinary catheter	• Urethral stricture • Benign prostatic hyperplasia • Bladder diverticulum • Cystocele • Calyceal diverticulum • UPJ obstruction

Table 4.10: Most important species of urease-producing bacteria

Obligate urease-producing bacteria (> 98%)
• *Proteus spp.* • *Providencia rettgeri* • *Morganella morganii* • *Corynebacterium urealyticum* • *Ureaplasma urealyticum*
Facultative urease-producing bacteria
• *Enterobacter gergoviae* • *Klebsiella spp.* • *Providencia stuartii* • *Serratia marcescens* • *Staphylococcus spp.*
CAUTION: *0-5% of Escherichia coli, Enterococcus spp. and Pseudomonas aeruginosa strains may produce urease.*

Figure 4.8: Diagnostic and therapeutic algorithm for infection stones



[1] *Discussed with uric acid stones.*
[2] *Acetohydroxamic acid*
** When nationally available.*
bid = twice a day; tid = three times a day; AHA = acetohydroxamic acid.

4.9 Cystine stones

Cystine stones account for 1-2% of all urinary stones in adults and 6-8% of the stones reported in paediatric studies [36, 659]. All cystine stone formers are deemed at high risk of recurrence and CKD [660, 661].

4.9.1 ***Diagnosis***

Blood analysis includes measurement of creatinine, and urinalysis includes measurement of urine volume, pH profile, specific weight, and cystine.

Interpretation

- Cystine is poorly soluble in urine and crystallises spontaneously within the physiological urinary pH range.
- Cystine solubility depends strongly on urine pH: at pH 6.0, the limit of solubility is 1.33 mmol/L.
- Routine analysis of cystine is not suitable for therapeutic monitoring.
- Regardless of phenotype or genotype of the cystinuric patient, the clinical manifestations are the same [662].
- There is no role for genotyping patients in the routine management of cystinuria [663, 664].
- Reductive therapy targets the disulphide binding in the cystine molecule. For therapy monitoring, it is essential to differentiate between cystine, cysteine and drug-cysteine complexes. Only high-performance liquid chromatography (HPLC)-based analysis differentiates between the different complexes formed by therapy.
- Diagnosis is established by stone analysis. The typical hexagonal crystals are detectable in only 20-25% of urine specimens from patients with cystinuria [665].
- The cyanide nitroprusside colorimetric qualitative test detects the presence of cystine at a threshold concentration of 75 mg/L, with a sensitivity of 72% and specificity of 95%. False-positive results in patients with Fanconi's syndrome, homocystinuria, or those taking various drugs, including infection stones [666].
- Quantitative 24-hour urinary cystine excretion confirms the diagnosis in the absence of stone analysis.
- Levels above 0.125 mmol/day (30 mg/day) are considered abnormal [667, 668].

4.9.2 ***Specific treatment***

General preventative measures for fluid intake and diet are recommended. A diet low in methionine may theoretically reduce urinary excretion of cystine; however, patients are unlikely to comply sufficiently with such a diet. A restricted intake of sodium is more easily achieved and is more effective in reducing urinary cystine. Patients are usually advised to avoid sodium consumption > 2 g/day (5 g NaCl) [669]. A high level of diuresis is of fundamental importance, aiming for a 24-hour urine volume of > 3 L [662, 665, 669, 670]. A considerable fluid intake evenly distributed throughout the day is necessary.

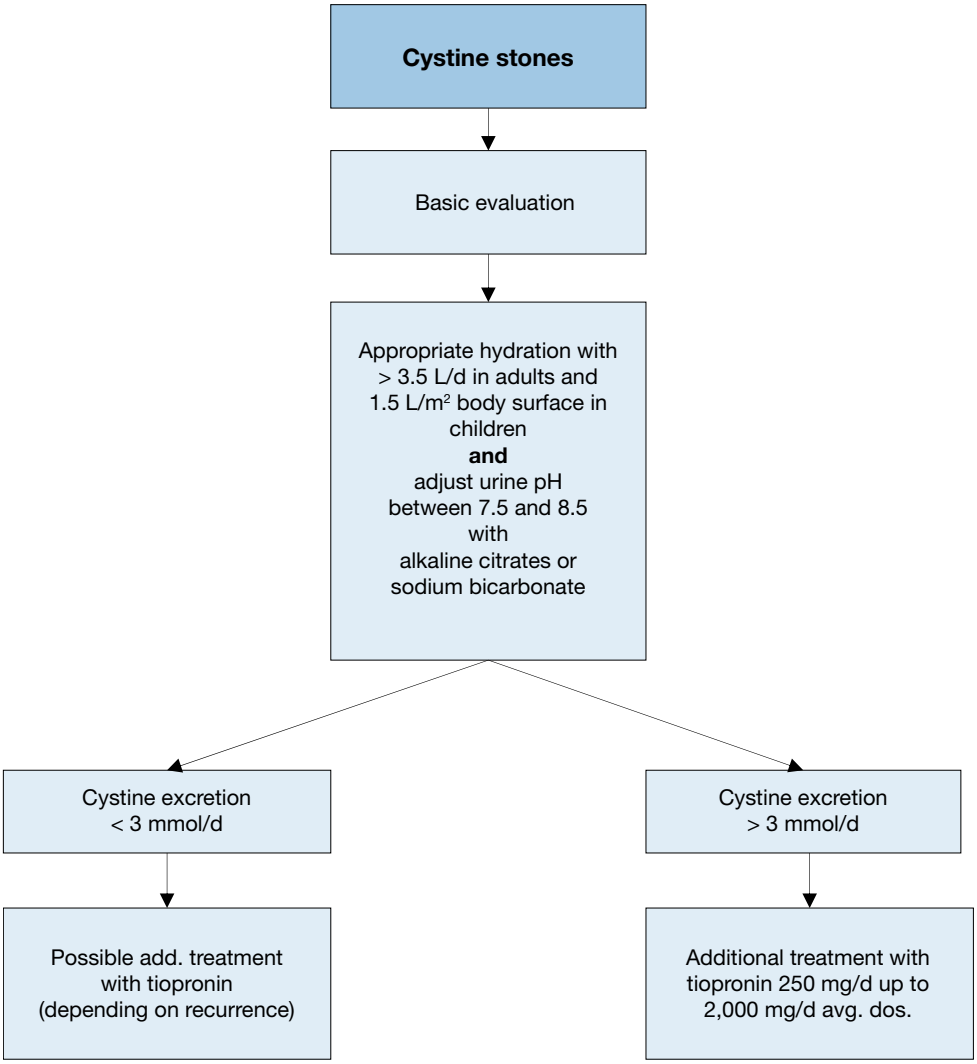
4.9.2.1 Pharmacological treatment of cystine stones

The main therapeutic option for avoiding cystine crystallisation is to maintain urine pH > 7.5, to improve cysteine solubility and ensure appropriate hydration with a minimum of 3.5 L/day in adults, or 1.5 L/m^2 body surface area in children [662, 665, 669, 670].

Free cystine concentration can be decreased by reductive substances, which act by splitting the disulphide binding of cystine.

Tiopronin is currently the best choice for cystine reduction. However, side effects often lead to treatment termination, for example when nephrotic syndrome develops or when there is poor compliance, especially with long-term use. After carefully considering the risk of early tachyphylaxis, put into place a dose-escape phenomenon for long-term use, and recurrence risk, tiopronin is recommended at cystine levels > 3.0 mmol/day (720 mg/day) or in the case of recurring stone formation, notwithstanding other preventive measures [662, 665, 669, 670].

Figure 4.9: Metabolic management of cystine stones


Cystine stones
Basic evaluation
Appropriate hydration with > 3.5 L/d in adults and 1.5 L/m² body surface in children
and
adjust urine pH between 7.5 and 8.5 with alkaline citrates or sodium bicarbonate
Cystine excretion < 3 mmol/d
Cystine excretion > 3 mmol/d
Possible add. treatment with tiopronin (depending on recurrence)
Additional treatment with tiopronin 250 mg/d up to 2,000 mg/d avg. dos.

4.9.3 Summary of evidence and guidelines for the management of cystine stones

Summary of evidence	**LE**
Increasing fluid intake so that 24-hour urine volume exceeds 3 L is used to dilute the cystine.	3
Alkaline citrates 3-10 mmol two or three times daily can be used to achieve pH > 7.5.	3
Tiopronin, 250-2,000 mg/day can be used to reduce stone formation in patients with cysteine excretion, > 3 mmol/day, or when other measures are insufficient.	3

Recommendations	**Strength rating**
Therapeutic measures	
Urine dilution Advise patients to increase their fluid intake so that 24-hour urine volume exceeds 3 L.	Strong
Alkalinisation Prescribe potassium citrate 3-10 mmol two or three times daily, to achieve pH > 7.5 for patients with cystine excretion < 3 mmol/day.	Strong
Complex formation with cystine For patients with cystine excretion, > 3 mmol/day, or when other measures are insufficient: prescribe in addition to other measures tiopronin, 250-2,000 mg/day.	Strong

4.10 2,8-Dihydroxyandenine stones and xanthine stones

All 2,8-Dihydroxyadenine and xanthine stone formers are considered to be at high risk of recurrence. Both stone types are rare. Diagnosis and specific prevention are similar to those for uric acid stones [25].

*4.10.1 **2,8-Dihydroxyadenine stones***

A genetically determined defect of adenine phosphoribosyl transferase causes high urinary excretion of poorly soluble 2,8-Dihydroxyadenine [671]. High-dose allopurinol or febuxostat are important options but should be given with regular monitoring [672].

*4.10.2 **Xanthine stones***

Patients who form xanthine stones usually show decreased levels of serum uric acid. There is no available pharmacological intervention.

*4.10.3 **Fluid intake and diet***

Recommendations for general preventive measures apply. Pharmacological intervention is difficult; therefore, high fluid intake ensures optimal specific weight levels of urine < 1.010 (urine specific gravity). A purine-reduced diet decreases the risk of spontaneous crystallisation in urine.

4.11 Drug-induced stones

Drug stones are induced by pharmacological treatment [583, 673] (Table 4.10). Two types exist:

- stones formed by crystallised compounds of the drug;
- stones formed due to unfavourable changes in urine composition under drug therapy.

Table 4.11: Compounds that cause drug stones

Active compounds crystallising in urine	Substances impairing urine composition
• Allopurinol/oxypurinol • Amoxicillin/ampicillin • Ceftriaxone • Quinolones • Ephedrine • Indinavir and other HIV-protease inhibitors • Magnesium trisilicate • Sulphonamides • Triamterene	• Acetazolamide • Allopurinol • Aluminium magnesium hydroxide • Ascorbic acid • Calcium • Furosemide • Laxatives • Losartan • Methoxyflurane • Orlistat • Vitamin D • Topiramate • Zonisamide

4.12 Matrix Stones

Pure matrix stones are extremely rare with less than 70 cases described in the literature. They are more prevalent in females. The main risk factors are recurrent UTIs, especially due to *P. mirabilis* or *E. coli*, previous surgery for stone disease, chronic renal failure, and haemodialysis. Complete endourological removal, frequently via the percutaneous approach, is critical. Given the rarity of matrix calculi a specific prophylactic regimen to minimise recurrence cannot be recommended. Eliminating infections and prophylactic use of antibiotics are most commonly proposed [674].

4.13 Unknown stone composition [18]

An accurate medical history is the first step towards identifying risk factors as summarised below (see section 4.13.1).

Diagnostic imaging begins with US examination of both kidneys to establish whether the patient is stone free. Stone detection by US should be followed by KUB and unenhanced multislice CT in adults to differentiate between calcium-containing and non-calcium stones.

Blood analysis demonstrates severe metabolic and organic disorders, such as renal insufficiency, HPT or other hypercalcaemic states and hyperuricaemia. In children, hyperoxalaemia should additionally be screened for.

Urinalysis is performed routinely with a dipstick test as described above. Urine culture is required if there are signs of infection. Constant urine pH < 5.8 in the daily profile may indicate acidic arrest, which

could promote uric acid crystallisation. Persistent urine pH > 5.8 in the daily profile may indicate RTA, if UTI is excluded [629, 631].

Microscopy of urinary sediment can help to discover rare stone types because crystals of 2,8-Dihydroxyadenine, cystine and xanthine are pathognomonic for the corresponding disease. In cases in which the presence of cystine is doubtful, a cyanide nitroprusside colorimetric qualitative test can be used to detect the presence of cystine in urine, with a sensitivity of 72% and specificity of 95%. False-positive results are possible in patients with Fanconi's syndrome or homocystinuria, or in those taking various drugs, including ampicillin or sulfa-containing medication [666, 675].

Following this programme, the most probable stone type can be assumed, and specific patient evaluation can follow. However, if any expulsed stone material is available, it should be analysed by diagnostic confirmation or correction.

*4.13.1 **Recommendations for investigations for the assessment of patients with stones of unknown composition*** [19, 25, 67, 583]

Recommendations		**Strength rating**
Investigation	**Rationale for investigation**	
Take a medical history	• Stone history (former stone events, family history) • Dietary habits • Medication chart	Strong
Perform diagnostic imaging	• Ultrasound in the case of a suspected stone • Un-enhanced helical computed tomography • Determination of Hounsfield units provides information about the possible stone composition	Strong
Perform a blood analysis	• Creatinine • Calcium (ionised calcium or total calcium + albumin) • Uric acid	Strong
Perform a urinalysis	• Urine pH profile (measurement after each voiding, minimum four times daily) • Dipstick test: leukocytes, erythrocytes, nitrites, protein, urine pH, specific weight • Urine cultures • Microscopy of urinary sediment (morning urine) • Cyanide nitroprusside test (cystine exclusion) Further examinations depend on the results of the investigations listed above.	Strong

5. FOLLOW-UP OF URINARY STONES

Patients suffering from urolithiasis have a predisposition to develop symptoms, complications, and recurrence of stones. Despite the rich literature published on urolithiasis very little has been written about how urolithiasis patients should be monitored after their treatment.

There is no general agreement on whether and when stone patients should be released from follow-up, nor when and how follow-up should occur for patients who need it. The main reason for this lack of agreement is the great clinical heterogeneity of stone disease among patients.

The Panel performed a systematic review questioning the benefits and harms of scheduled follow-up for patients who underwent definitive treatment (ESWL, URS, PNL, medical chemoprophylaxis) for upper urinary tract stone disease [676] .

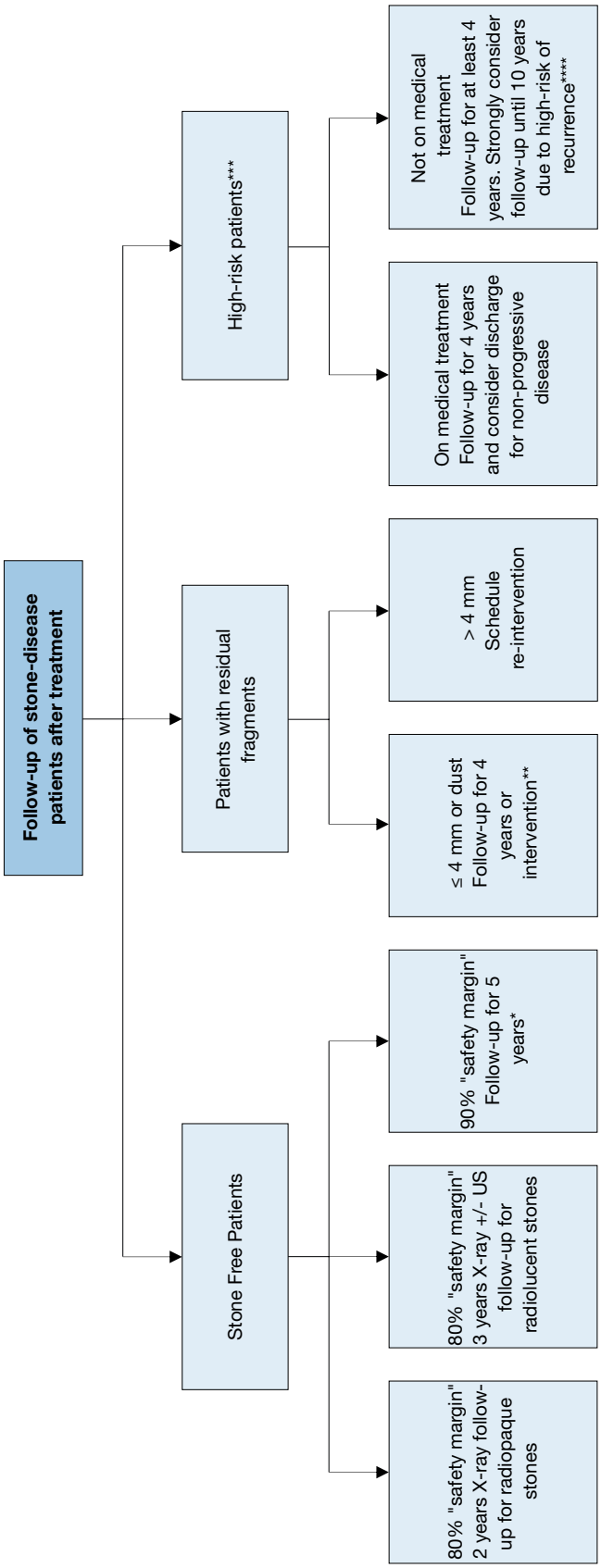
The Panel aimed to answer three main questions regarding urolithiasis follow-up: a) In patients with no residual fragments, does imaging follow-up after treatment for upper urinary tract stones offer more clinical benefits than harms compared with no scheduled follow-up?; b) In patients with residual fragments, does imaging follow-up after treatment for upper urinary tract stones offer more clinical benefits than harms compared with

no scheduled follow-up?; and c) Does biochemical urine analysis follow-up after treatment for upper urinary tract stones offer more clinical benefits than harms compared with no scheduled follow-up? There was a lack of comparative studies regarding follow-up vs. no follow-up, so the primary endpoints were not reached. The Panel used the data from the eligible observational and randomised studies included in the systematic review to identify the time of patient discharge after follow-up according to stone disease status (stone-free patients, patients with residual stones, patients with metabolic abnormalities), and to come to a consensus on frequency of follow-up and use of investigations.

From a pooled analysis of 5,467 stone-free patients, the Panel estimated that for a safety margin of 80%, patients should be followed-up using imaging, for at least two years (radiopaque stones), or at least three years (radiolucent stones) before discharge, while for a safety margin of 90% patients should be discharged after five years of no recurrence. Regarding residual disease, patients with fragments ≤ 4 mm could be offered surveillance for up to four years, since intervention rates range between 17-29%, disease progression between 9-34%, and spontaneous passage between 21-34% at 49 months. Patients with larger residual fragments should be offered further definitive intervention, since intervention rates are high (24-100%). Insufficient data exist for high-risk patients, but current literature dictates that patients who are adherent to targeted medical treatment seem to experience less stone growth or re-growth of residual fragments and may be discharged after 36-48 months of non-progressive disease on imaging (Figure 5.1).

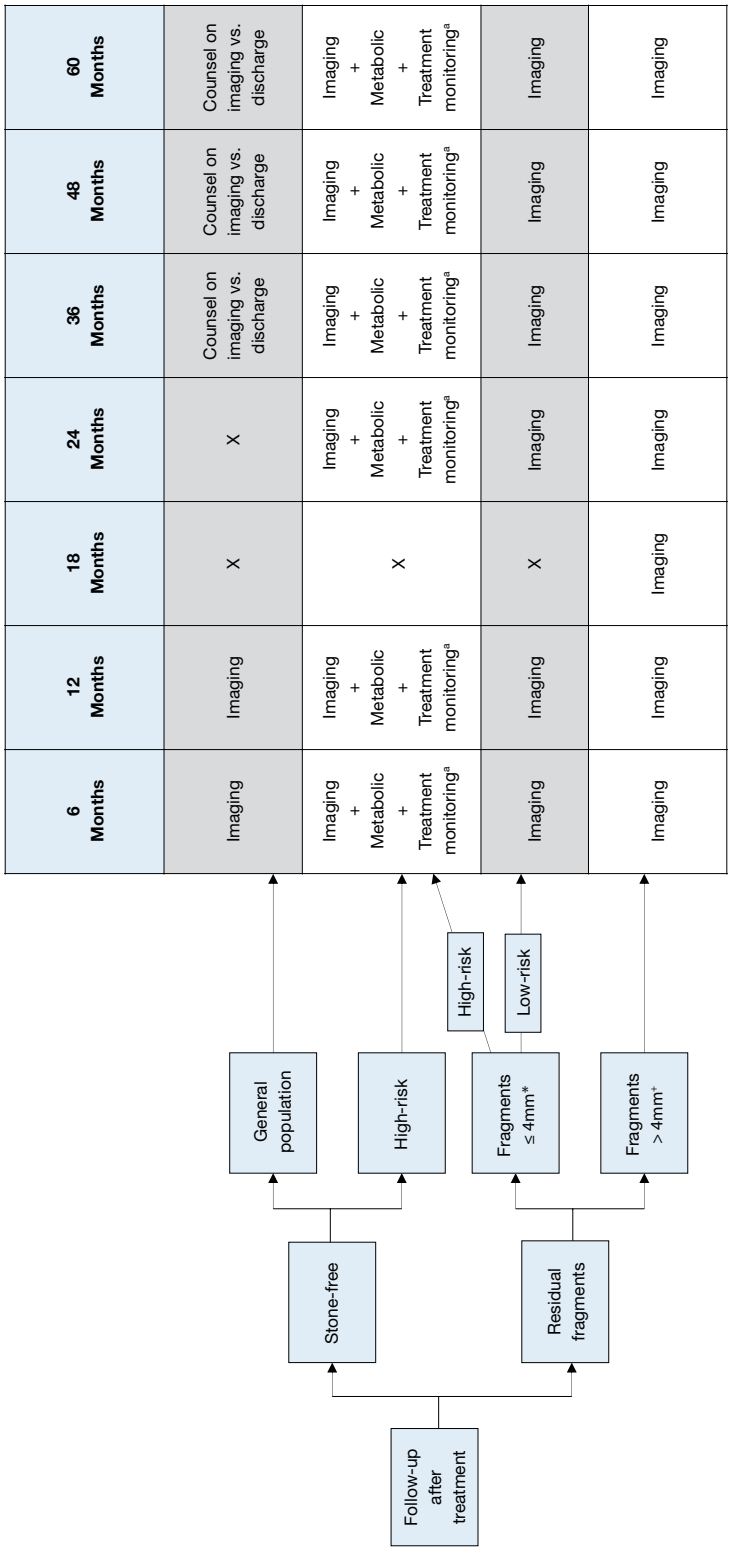
A Panel consensus was reached after extensive discussion of data regarding frequency of follow-up. In stone-free general population, the vast majority of patients remained stone-free during the first year, in contrast with patients with metabolic abnormalities not under targeted medical treatment < 40% were stone-free after three years of follow-up. Therefore, a more extensive follow-up is proposed for patients with metabolic abnormalities. Patients with small residual fragments ≤ 4 mm, showed a spontaneous expulsion at 17.9-46.5% and growth rate at 10.1-40.7% during the first year, while patients with larger fragments (> 4 mm) had only 9% of spontaneous expulsion at three years. Therefore, patients with small ≤ 4 mm, asymptomatic fragments should be followed-up or scheduled for an intervention according to patient preference, while those with larger stones should primarily be offered re-intervention. Proposed imaging consists of plain X-ray KUB and/or US, based on stone characteristics and clinicians' preferences. Computed tomography scan should be reserved for symptomatic disease or pre-operative imaging, in order to avoid extensive radiation exposure (Figure 5.2) [676].

Figure 5.1: Follow-up duration of urinary stone patients after treatment


Follow-up of stone-disease patients after treatment
High-risk patients***
Not on medical treatment Follow-up for at least 4 years. Strongly consider follow-up until 10 years due to high-risk of recurrence****
On medical treatment Follow-up for 4 years and consider discharge for non-progressive disease
Patients with residual fragments
> 4 mm Schedule re-intervention
≤ 4 mm or dust Follow-up for 4 years or intervention**
Stone Free Patients
90% "safety margin" Follow-up for 5 years*
80% "safety margin" 3 years X-ray +/- US follow-up for radiolucent stones
80% "safety margin" 2 years X-ray follow-up for radiopaque stones

** Not enough data about subgroup analysis of radiolucent and radiopaque stones.*
*** According to patient preference or symptomatic disease.*
**** Patients with diagnosed metabolic abnormalities.*
***** Lifelong follow-up is advised but data are available up to 10 years.*

Figure 5.2: Consensus on follow-up frequency and imaging modality to use after treatment



Stone free = No stone fragments on post-operative imaging (i.e. no stone fragments on CT/KUB/US). High-risk = Known biochemical abnormality (i.e,: hypercalciuria, hypocitraturia, hyperuricosuria, RTA or high-risk stone type such as struvite). Imaging = plain film KUB &/or kidney ultrasonography (KUS) based on clinicians' preference and stone characteristics. Consider CT if patient is symptomatic or if intervention is planned.

** Clinicians may choose the imaging-only pathway in patients with fragments ≤ 2 mm.*
º Treatment monitoring for side effects, intolerance, and compliance.
+ Panel recommends re-intervention however close follow up may be considered for some patients at high risk for re-intervention based on clinicians' preference.

6. BLADDER STONES

6.1 Prevalence, aetiology, and risk factors of bladder stones

Bladder stones constitute only approximately 5% of all urinary tract stones [677] yet are responsible for 8% of urolithiasis-related mortalities in developed nations [678]. The incidence is higher in developing countries [679]. The prevalence of bladder stones is higher in males, with a reported male to female ratio between 10:1 and 4:1 [680, 681]. The age distribution is bimodal: incidence peaks at three years in children in developing countries [680, 682], and 60 years in adulthood [681].

The aetiology of bladder stones is typically multi-factorial [681]. Bladder stones can be classified as primary, secondary, or migratory [683].

Primary or endemic bladder stones occur in the absence of other urinary tract pathology, typically seen in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein [684].

Secondary bladder stones occur in the presence of other urinary tract abnormalities, which include bladder outlet obstruction (BOO), neurogenic bladder dysfunction, chronic bacteriuria, foreign bodies (including catheters), bladder diverticula and bladder augmentation or urinary diversion. In adults, BOO is the most common predisposing factor for bladder stone formation and accounts for 45-79% of vesical calculi [681, 685-688].

Migratory bladder stones are those which have passed from the upper urinary tract where they formed and may then serve as a nidus for bladder stone growth. Patients with bladder calculi are more likely to have a history of upper tract stones and risk factors for their formation [689].

A wide range of metabolic urinary abnormalities can pre-dispose to calculi anywhere in the urinary tract, which is covered in more detailed in section 4. Metabolic Evaluation and Recurrence Prevention. There is a paucity of studies on the specific metabolic abnormalities which predispose to bladder stones.

Bladder stones will form in 3-4.7% of men undergoing surgery for benign prostatic obstruction (BPO) [690, 691], 15-36% of spinal cord injury patients [692-694], and 2.2% of patients with long-term catheters [695]. Of 57 men with chronic urinary retention secondary to BPO, the urine of the 30 men with bladder stones had a higher uric acid concentration (2.2 vs. 0.6 mmol/L, $p < 0.01$), lower magnesium (106 vs. 167 mmol/L, $p = 0.01$) and lower pH (5.9 vs. 6.4, $p = 0.02$) than the 27 men without bladder stones [689]. It is therefore likely that patients with these conditions who form bladder stones also have an abnormal urine composition which pre-disposes them to bladder stone formation.

The metabolic abnormalities which pre-dispose patients to form secondary bladder stones are poorly understood. Stone analysis of 86 men with a BPO-related bladder stone demonstrated 42% had calcium-based stones (oxalate, phosphate), 33% had magnesium ammonium phosphate, 10% had mixed stones and 14% had urate stones [681]. Similar findings were reported in more recent studies [696-698] and it is therefore likely that multiple metabolic factors pre-dispose patients to secondary bladder stone formation.

The exact metabolic basis for primary bladder stones is poorly understood and likely multi-factorial. Low urine volume (poor hydration) is the most consistently demonstrable abnormality [699-701]. Twenty-four-hour urine analysis in children with endemic bladder stones is reported in two studies. Of 57 children in Pakistan, 89.5% had hypocitraturia, 49% had a low urine volume, 44% had hyperoxaluria and 42% had hypocalciuria [699]. Of 61 children in India, stone formers had higher urine calcium and uromucoid concentrations than controls [700]. One study from Thailand compared 24-hour urine analyses from children from a rural area with a high prevalence of bladder stones with those from an urban area: rural children had lower urine volumes and, despite equal calcium, oxalate, and uric acid concentrations, crystalluria with uric acid and calcium oxalate crystals was more prevalent in rural children [701].

Table 6.1 Bladder stones classified by aetiology

Type of bladder stone	Primary	Secondary	Migratory
Cause/Associations	Occur in the absence of other urinary tract pathology, typically in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein	BOO (e.g., BPO, urethral stricture)	Form in the upper urinary tract, then passed into the bladder where they may be a nidus for stone growth
		Neurogenic bladder dysfunction	
		Chronic bacteriuria	
		Foreign bodies (including catheters)	
		Bladder diverticula	
		Bladder augmentation	
		Urinary diversion	

BOO = bladder outlet obstruction; BPO = benign prostatic obstruction.

6.2 Presentation

The symptoms most commonly associated with bladder stones are urinary frequency, haematuria (which is typically terminal) and dysuria or suprapubic pain, which are worst towards the end of micturition. Sudden movement and exercise may exacerbate these symptoms. Detrusor over-activity is found in over two thirds of adult male patients with vesical calculi and is significantly more common in patients with larger stones (> 4 cm). However, recurrent UTIs may be the only symptom [686, 687].

In children, symptoms may also include pulling of the penis, difficulties in micturition, urinary retention, enuresis and rectal prolapse (resulting from straining due to bladder spasms). Bladder stones may also be an incidental finding in 10% of cases [684, 702].

6.3 Diagnostic evaluation

*6.3.1 **Diagnostic investigations for bladder stones***

Plain X-ray of KUB has a reported sensitivity of 21%-78% for cystoscopically detected bladder stones in adults [686, 703]. Larger (> 2.0 cm) stones are more likely to be radiopaque [703]. However, plain X-ray provides information on radio-opacity which may guide treatment and follow-up (see section 3.2.3 X-ray characteristics, for further information).

Ultrasound has a reported sensitivity and specificity of 20-83% and 98-100%, respectively for the detection of bladder stones in adults [704, 705]. Computed tomography and cystoscopy have a higher sensitivity for detecting bladder stones than US or X-Ray in adults [704, 705]. No study compares cystoscopy and CT for the diagnosis of bladder stones. Cystoscopy has the advantage of detecting other potential causes for a patient's symptoms (e.g., bladder cancer), whilst CT can also assess upper tract urolithiasis (see section 3.2.3 X-ray characteristics) [706] .

There is a paucity of evidence for the investigation of bladder stones, particularly in children [84, 707]. See also section 3.3 Diagnostic evaluation, for further information on diagnostic imaging for urolithiasis. The principle of ALARA should be applied, especially in children [708].

*6.3.2 **Diagnosing the cause of bladder stones***

The cause of the bladder stone should be considered prior to bladder stone treatment as eliminating the underlying cause will reduce recurrence rates [709]. The following should be performed where possible prior to (or at the time of) bladder stone treatment:

- physical examination of external genitalia, peripheral nervous system (including digital rectal examination, peri-anal tone, and sensation in men);
- uroflowmetry and post-void residual urine assessment;
- urine dipstick to include pH ± culture;
- metabolic assessment (see section 3.3.2.3) including: serum (creatinine, (ionised) calcium, uric acid, sodium, potassium, blood cell count);
- urine pH;
- stone analysis: in first-time formers using a valid procedure (X-ray diffraction or infrared spectroscopy).

The following investigations should also be considered for selected patients:

- upper tract imaging (in patients with a history of urolithiasis or loin pain);
- cysto-urethroscopy or urethrogram.

6.4 Disease Management

6.4.1 ***Conservative treatment and Indications for active stone removal***

Migratory bladder stones in adults may typically be left untreated, especially asymptomatic small stones. Rates of spontaneous stone passage are unknown, but data on ureteric stones suggest stones < 1 cm are likely to pass in the absence of BOO, bladder dysfunction or long-term catheterisation (see section 3.4.9 Specific stone management of ureteral stones).

Primary and secondary bladder stones are usually symptomatic and are unlikely to pass spontaneously: active treatment of such stones is usually indicated.

6.4.2 ***Medical management of bladder stones***

There is a paucity of evidence on chemolitholysis of bladder stones. However, guidance on the medical management of urinary tract stones in section 3.4.9 Specific stone management of ureteral stones, can be applied to urinary stones in all locations. Uric acid stones can be dissolved by oral urinary alkalinisation when a PH > 6.5 is consistently achieved, typically using an alkaline citrate or sodium bicarbonate. Regular monitoring is required during therapy (see section 3.4.4 Chemolysis). Irrigation chemolysis is also possible using a catheter; however, this is time consuming and may cause chemical cystitis and is therefore not commonly employed [141, 710].

6.4.3 ***Bladder stone interventions***

Minimally invasive techniques for the removal of bladder stones have been widely adopted to reduce the risk of complications and shorten hospital stay and convalescence. Bladder stones can be treated with open, laparoscopic, robotic assisted laparoscopic, endoscopic (transurethral or percutaneous) surgery or ESWL [4].

6.4.3.1 Suprapubic cystolithotomy

Open suprapubic cystolithotomy is very effective but is associated with a need for catheterisation and longer hospital stay in both adults and children compared to all other stone removal modalities [360]. In children, a non-randomised study found that, if the bladder was closed meticulously in two layers, “tubeless” (drain-less and catheter-less) cystolithotomy was associated with a significantly shorter length of hospital stay compared with traditional cystolithotomy, without significant differences regarding late or intra-operative complications provided that children with prior UTI, recurrent stones, or with previous surgery for anorectal malformation (or other relevant surgery) were excluded [711].

6.4.3.2 Transurethral cystolithotripsy

In both adults and children, transurethral cystolithotripsy provides high SFRs and appears to be safe, with a very low-risk of unplanned procedures and major post-operative and late complications [4].

6.4.3.2.1 Transurethral cystolithotripsy in adults

In adults, meta-analysis of four RCTs including 409 patients demonstrated that transurethral cystolithotripsy has a shorter hospital stay and convalescence with less pain, but equivalent SFR and complications compared to percutaneous cystolithotripsy [4]. Transurethral cystolithotripsy with a nephroscope was quicker than percutaneous cystolithotripsy in three RCTs, although transurethral cystolithotripsy with a cystoscope was slower than percutaneous cystolithotripsy [4].

Rates of urethral strictures following transurethral procedures were not robustly reported: studies report rates between 2.9% and 19.6% during a follow up of 12 – 24 months [4, 696, 712].

One small RCT demonstrated a shorter duration of catheterisation, hospital stay and procedure with transurethral cystolithotripsy than open cystolithotomy with similar SFR [4]. Meta-analysis of four RCTs found shorter procedure duration for transurethral cystolithotripsy using a nephroscope vs. cystoscope with similar SFRs, hospital stay, convalescence, pain, and complications [4, 696, 713-715]. Two retrospective studies (n=188) reported that using a resectoscope or nephroscope was associated with a shorter procedure duration ($p < 0.05$) than a cystoscope for transurethral cystolithotripsy [716, 717]. This suggests that transurethral cystolithotripsy is quicker when using a continuous flow instrument.

6.4.3.2.1.1 Lithotripsy modalities used during transurethral cystolithotripsy in adults

When considering lithotripsy modalities for transurethral cystolithotripsy, the Panel’s systematic review found very low-quality evidence from five non-randomised studies (n=385) which found no difference in SFR between modalities (mechanical, laser, pneumatic, ultrasonic, electrohydraulic lithotripsy [EHL] or washout alone) [4]. Unplanned procedures and major post-operative complications were low-rate events and were not significantly different between lithotripsy modalities, although one non-randomised study (NRS) suggested these might be

higher with EHL or mechanical lithotripsy than pneumatic or ultrasonic lithotripsy [718]. All outcomes had very low-quality of evidence (GRADE) [4]. High powered lasers seem to reduce lithotripsy time. Laser lithotripsy was faster than pneumatic lithotripsy (MD 16.6 minutes; CI: 23.51-9.69, p < 0.0001) in one NRS (n=62); however, a laser was used with a resectoscope and the pneumatic device with a cystoscope [719]. Continuous vs. intermittent irrigating instrument may affect the operation time more significantly than the choice of lithotripsy device [4].

6.4.3.2.1.2 Transurethral cystolithotripsy in children
In children, three NRS suggest that transurethral cystolithotripsy has a shorter hospital stay and catheterisation time than open cystolithotomy, but similar stone-free and complication rates [4, 720]. One small quasi RCT found a shorter procedure time using laser vs. pneumatic lithotripsy for < 1.5 cm bladder stones with no difference in SFR or other outcomes [4, 721].

6.4.3.3 Percutaneous cystolithotripsy
6.4.3.3.1 Percutaneous cystolithotripsy in adults:
One NRS found a shorter duration of procedure and catheterisation and less blood loss for percutaneous, compared with open surgery in adult male patients with urethral strictures; all patients in both groups were rendered stone-free [698].

Meta-analysis of four RCTs comparing transurethral and percutaneous cystolithotripsy found a shorter hospital stay for transurethral cystolithotripsy over percutaneous surgery. Transurethral cystolithotripsy was quicker when using a nephroscope. There were no significant differences in SFRs, major post-operative complications or re-treatment [4].

6.4.3.3.2 Percutaneous cystolithotripsy in children:
In children, three NRS suggest that percutaneous cystolithotripsy has a shorter hospital stay and catheterisation time, but a longer procedure duration and more peri-operative complications than open cystolithotripsy; SFRs were similar [4, 702, 720].

Two small NRS compared percutaneous and transurethral cystolithotripsy and both found similar SFRs, but that transurethral surgery offers a shorter duration of catheterisation and hospital stay [702, 720]. One small NRS found a non-significant increased risk of unplanned procedures (within 30 days of primary procedure) and major post-operative complications for percutaneous operations compared with transurethral procedures; however, age and stone size determined which intervention children underwent and all patients were rendered stone-free [702]. Urethral stricture rates were not robustly compared in either study.

6.4.3.4 Extracorporeal shock wave lithotripsy
Extracorporeal SWL is the least invasive therapeutic procedure [4].

6.4.3.4.1 Shock wave lithotripsy in adults
In adults, one RCT compared SWL with transurethral cystolithotripsy in 100 patients with ≤ 2 cm bladder stones presenting with acute urinary retention. Stone free rate after one SWL session favoured transurethral cystolithotripsy (86% vs. 98%, p=0.03); however, following up to three sessions of SWL, there was no significant difference in SFR (94% vs. 98%, p=0.3) [4, 722].

Two NRS compared transurethral cystolithotripsy vs. SWL and found no significant difference in SFR (97.0% vs. 93.9%, p=0.99, 97.7% vs. 89.7% p=0.07) despite larger stones in transurethral cystolithotripsy patients (4.2 vs. 2.5 cm, p=0.014; and 3.6 vs. 2.6 cm [p value not reported]) [723, 724].

Length of hospital stay appeared to favour SWL in all three studies (0 vs. 1 day, 4.8 vs. 0 days, p=0.02, 0.8 vs. 2.4 days, respectively) [722-724]. No significant differences in major post-operative or intra-operative complications were reported in any study [722-724].

One NRS compared SWL vs. open cystolithotomy in just 43 patients. Stone sizes were not comparable (2.5 vs. 7.4 cm, p < 0.001). Stone-free rates were not significantly different (93.9% vs. 100%, p=0.50). Length of stay favoured SWL. There was no significant difference in intra-operative or major post-operative complications [723].

6.4.3.4.2 Shock wave lithotripsy in children
One large NRS found lower SFR for SWL than both transurethral cystolithotripsy and open cystolithotomy,

despite treating smaller stones with SWL. However, the length of hospital stays favoured SWL over open cystolithotomy, although this appeared to be comparable between SWL and transurethral cystolithotripsy [725].

6.4.3.5 Laparoscopic cystolithotomy

Laparoscopic cystolithotomy has been described in adults and is typically performed in combination with simple prostatectomy using either traditional laparoscopy or with robotic assistance [726, 727]. A SR found no studies comparing laparoscopic surgery with other procedures [4].

6.4.4 ***Treatment for bladder stones secondary to bladder outlet obstruction in adult men***

Bladder stones in men aged over 40 years may be caused by BPO, the management of which should also be considered. Bladder stones were traditionally an indication for a surgical intervention for BPO: a doctrine which has been questioned by recent studies. One prospective study reports urodynamics (cystometrogram) findings in 46 men aged > 60 years before and after bladder stone treatment [687]. Only 51% of men had BOO while 10% had detrusor under-activity. Eighteen percent of men had a completely normal urodynamic study and 68% had detrusor over-activity. There was no significant difference between pre- and post-bladder stone removal urodynamic findings [687].

One NRS compared 64 men undergoing transurethral cystolithotripsy with either transurethral resection of prostate (TURP) or medical management for BPO (α-blocker with or without 5-alpha reductase inhibitor). After 28 months follow-up, no men on medication had had a recurrence, but 34% underwent TURP: a high post-void residual urine volume predicted the need for subsequent TURP [728]. Another observational study of 23 men undergoing cystolithotripsy and commencing medical management for BPO found 22% developed a BPO related complication, including 17% who had recurrent stones [709].

Large studies support the safety of performing BPO and bladder stone procedures during the same operation with no difference in major complications compared to a BPO procedure alone [729-731]. An observational study on 2,271 patients undergoing TURP found no difference in complications except UTIs, which occurred slightly more frequently in patients with simultaneously treated bladder stones: 0% vs. 0.6%, p=0.044 [729]. An observational study of 321 men undergoing Holmium laser enucleation of the prostate (HoLEP) found a higher rate of early post-operative incontinence (26.8% vs. 12.5%, p=0.03) in men having concomitant transurethral cystolithotripsy, but no difference in long-term continence rates [731]. Another larger multicenter observational study of 963 patients undergoing HoLEP found no significant differences in frequency of complications in patients with (n=54 (5.6%)) or without concomitant transurethral cystolithotripsy [732].

6.4.5 ***Special situations***

6.4.5.1 Neurogenic bladder and stone formation

Patients with a neurogenic bladder secondary to spinal cord injury or myelomeningocele are at increased risk of forming bladder stones. Within eight to ten years, 15-36% of patients with spinal cord injury will develop a bladder stone [692-694]. The absolute annual risk of stone formation in spinal cord injury patients with an indwelling catheter is 4% compared with 0.2% for those voiding with clean intermittent self-catheterisation (CISC) [733].

A study of 2,825 spinal cord injury patients over eight years found a 3.3% incidence of bladder stones: 2% with CISC, 6.6% with indwelling urethral catheter, 11% with a suprapubic catheter and 1.1% in patients voiding using reflex micturition [734]. However, another study of 457 spinal cord injury patients for six months found no difference in bladder stones between urethral and suprapubic catheterisation [733]. Spinal cord injury patients with an indwelling urethral catheter are six times more likely to develop bladder stones than patients with normal micturition [694, 734].

The risk of stone recurrence after complete removal in spinal cord injury patients is 16% per year [733]. A RCT of 78 spinal cord injury patients who perform CISC found a significant reduction in bladder stone formation when twice weekly manual bladder irrigations were performed for six months (49% vs. 0%, p= < 0.0001), as well as less symptomatic UTIs (41% vs. 8%; p=0.001) [735]. However, this study excluded patients who developed autonomic dysreflexia during bladder irrigations. The irrigation volume used was not reported.

6.4.5.2 Bladder Augmentation

The incidence of vesical calculus formation after bladder augmentation is 2-44% in adults [736-745], and 4-53% in children [745-759]. Following cystoplasty, stones form after 24-31 months in adults [737, 739, 744], and after 25-68 months in children [750, 753, 754, 758, 760-762]. The reported cumulative incidence of bladder stone formation after ten years is 28-36% and after twenty years is 41% [745, 763].

Risk factors for bladder stone formation after augmentation include excess mucus production, incomplete bladder emptying, non-compliance with CIC or bladder irrigations, bacteriuria or urinary tract infections (due to urease-producing bacteria), foreign bodies (including staples, mesh, non-absorbable sutures), drainage by vesico-entero-cystostomy (Mitrofanoff or Monti) [436, 737, 740, 742, 743, 750, 754, 757, 763] and voiding by CISC compared with those voiding spontaneously [741]. Gastric segment augmentation confers a lower risk of bladder stones than ileal or colonic segment cystoplasty [746, 750, 754, 757].

In previous stone formers, the rate of recurrence is 15-44% in adults [737-739, 741, 744], and 19-56% in children [436, 745, 746, 750, 752-755, 757, 762]. The risk of recurrence is greatest during the first two years, at about 12% per patient per year, with the risk decreasing with time [762].

Daily, or three-times-weekly bladder irrigations reduce the incidence of bladder stones following bladder augmentation or continent urinary diversion [436, 740]. A randomised study found that daily bladder irrigation with 240 mL of saline reduced stone recurrences ($p = < 0.0002$, $p = 0.0152$) and symptomatic UTIs ($p < 0.0001$, $p < 0.0001$) compared to 60mL or 120mL [740]. The frequency of bladder irrigations required is unclear.

6.4.5.3 Urinary diversion

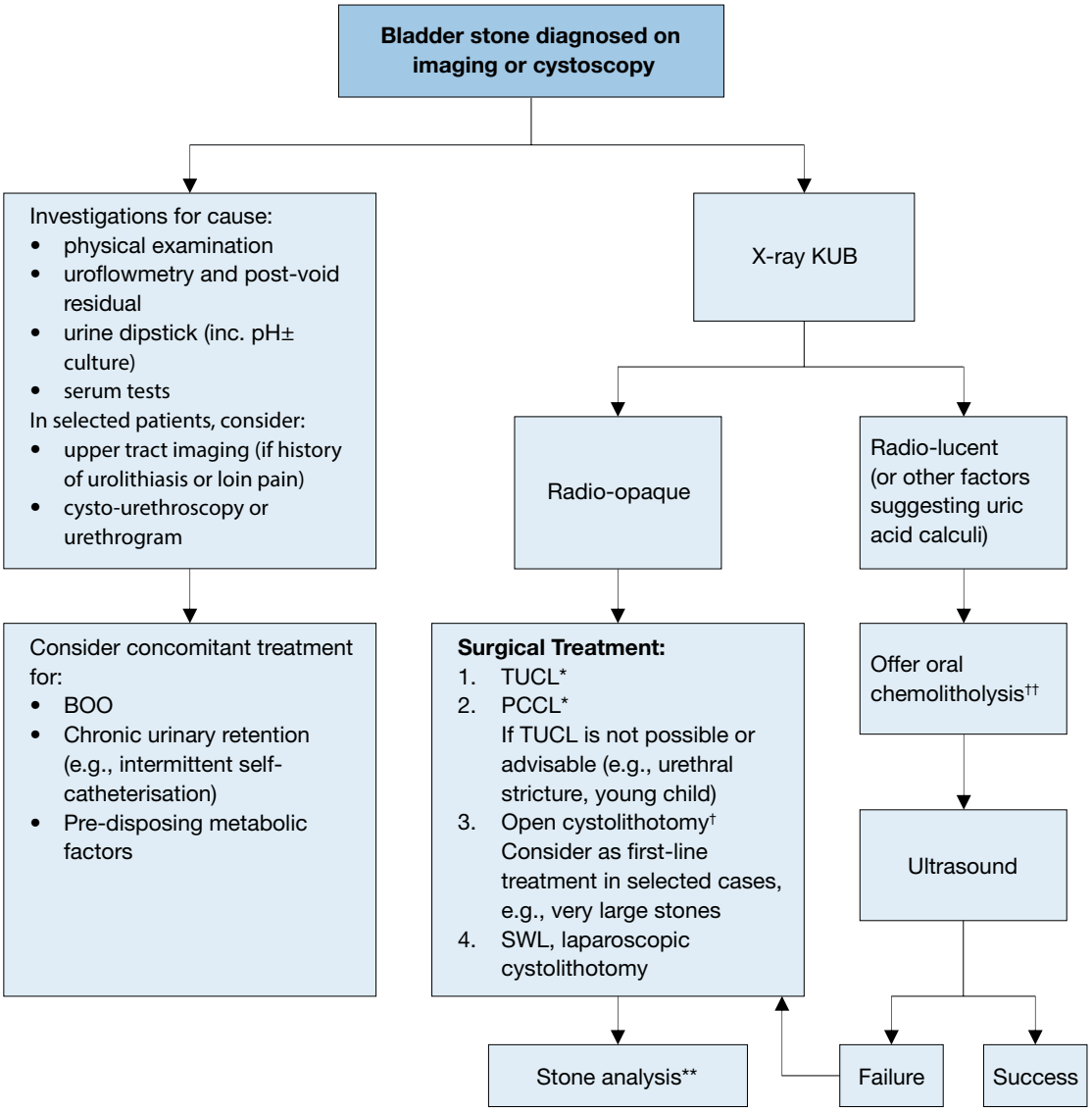
The incidence of stone formation after urinary diversion with an ileal or colon conduit is 0-3% [764, 765]. The incidence of stone formation is 0-34% in orthotopic ileal neobladders (Hautmann, hemi-Kock, Studer, T-pouch or w-neobladder) [741, 765-774], and 4-6% in orthotopic sigmoid neobladders (Reddy) [770, 775]. The risk of pouch stone formation is 4-43% in adults with an ileocaecal continent cutaneous urinary diversion (Indiana, modified Indiana, Kock or Mainz I) [428, 741, 764, 765, 773, 776]. The average interval from construction of the urinary diversion to stone detection is 71-99 months [769, 777]. In children, the incidence of neobladder stone formation is 30% after Mainz II diversion (rectosigmoid reservoir) [747], and 27% after Kock ileal reservoir construction [759].

6.4.5.4 Treatment of stones in patients with bladder augmentation or urinary diversion

Stones may be removed by open or endoscopic surgery in patients with bladder augmentation or diversion [752]. However, often access cannot be obtained through a continent vesico-entero-cystostomy without damaging the continence apparatus; hence a percutaneous or open approach is typically preferred [752].

No studies comparing outcomes following procedures for stones in reconstructed or augmented bladders were found. Two observational studies indicate that percutaneous lithotomy can be safely performed with US or CT guidance in patients with reconstructed or augmented bladders [778, 779] and is proposed to offer similar advantages over open surgery to those for percutaneous native bladder surgery. Stone recurrence after successful removal has been reported to be 10-42% [778, 779], but appears to be unrelated to the modality used for stone removal [744, 750, 754, 755, 757, 762].

Figure 6.1 Management of bladder stones


Bladder stone diagnosed on imaging or cystoscopy
Investigations for cause:
• physical examination
• uroflowmetry and post-void residual
• urine dipstick (inc. pH± culture)
• serum tests
In selected patients, consider:
• upper tract imaging (if history of urolithiasis or loin pain)
• cysto-urethroscopy or urethrogram
X-ray KUB
Radio-opaque
Radio-lucent (or other factors suggesting uric acid calculi)
Consider concomitant treatment for:
• BOO
• Chronic urinary retention (e.g., intermittent self-catheterisation)
• Pre-disposing metabolic factors
Surgical Treatment:
1. TUCL*
2. PCCL*
If TUCL is not possible or advisable (e.g., urethral stricture, young child)
3. Open cystolithotomy†
Consider as first-line treatment in selected cases, e.g., very large stones
4. SWL, laparoscopic cystolithotomy
Offer oral chemolitholysis††
Ultrasound
Stone analysis**
Failure
Success

BOO = bladder outlet obstruction, TUCL = trans-urethral cystolithotripsy, PCCL = percutaneous cystolithotripsy, SWL = shock-wave lithotripsy.

** Lithotripsy modality at surgeon's discretion (e.g., mechanical, laser, pneumatic, ultrasonic).*

† Prefer "tubeless" procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery, or bladder dysfunction where open cystolithotomy is indicated.

*** Stone analysis should be sent for all first-time stone formers and in patients who develop a recurrence under pharmacological prevention, early recurrence after interventional therapy with complete stone clearance or late recurrence after a prolonged stone-free period.*

†† Use an alkaline citrate or sodium bicarbonate with frequent urine pH monitoring and dose titration to achieve a consistent pH > 6.5.

6.5 Bladder stones follow-up

There are no studies examining the merits of differing follow-up modalities or frequencies following conservative, medical, or operative treatment of bladder stones in adults or children. Identification and prevention of the cause of bladder stone formation will be crucial to prevent recurrence (see section 6.3.2 Diagnosing the cause of bladder stones).

In adults, there is a paucity of evidence on dietary modification or medical treatment for the prevention of bladder stone recurrence. Recommendations in the EAU Guideline on Urolithiasis, based on evidence from upper tract stones, constitutes the best available recommendations, especially for migratory bladder stones (see section 4. Metabolic Evaluation and Recurrence Prevention).

Where it is possible to address the cause of secondary bladder stones (e.g., treatment of BPO), it is unclear whether metabolic intervention would offer any significant additional benefit in preventing stone recurrence. However, especially where the secondary cause cannot be addressed (e.g., indwelling catheter, neuropathic bladder, bladder augmentation or urinary diversion); metabolic interventions are likely to reduce bladder stone recurrence rates.

Regular bladder irrigation reduces the chances of bladder stone recurrence in adults and children with bladder augmentation or continent cutaneous urinary diversion and adults with spinal cord injury who perform CISC (see section 6.4.5 Special Situations) [735, 740, 765].

In children with primary (endemic) bladder stones maintenance of hydration, avoidance of diarrhoea and a mixed cereal diet with milk and Vitamins A and B supplements, with the addition of eggs, meat, and boiled cows' milk after one year of age are recommended to prevent recurrence [699].

Finally, there are contradictory reports on a possible association between bladder calculi and future development of bladder cancer [780-782]. The need for follow-up with regular cystoscopy therefore remains controversial.

Summary of evidence	**LE**
The incidence of bladder stones peaks at three years in children (endemic/primary stones in developing countries) and 60 years in adults.	2c
The aetiology of bladder stones is typically multi-factorial. Bladder stones can be classified as primary (endemic), secondary (associated with lower urinary tract abnormalities e.g., BPO, neuropathic bladder, foreign body, chronic bacteriuria) or migratory (having formed in the upper tract).	4
In adults, BOO is the most common pre-disposing factor for bladder stone formation.	2C
Of men undergoing surgery for BPO, 3-4.7% form bladder stones.	2b
Metabolic abnormalities are also likely to contribute to bladder stone formation in patients with secondary bladder stones.	2b
Primary (endemic) bladder stones typically occur in children in areas with poor hydration, recurrent diarrhoea, and a diet deficient in animal protein. The following measures are proposed to reduce their incidence: maintenance of hydration, avoidance of diarrhoea, and a mixed cereal diet with milk and Vitamins A and B supplements; with the addition of eggs, meat, and boiled cows' milk after one year of age.	5
In adults, US has a sensitivity of 20-83% for diagnosing bladder stones.	2b
In adults, X-ray-KUB has a sensitivity of 21-78%; sensitivity increases with stone size.	2b
Computed tomography has a higher sensitivity than US for the detection of bladder stones.	2b
Cystoscopy has a higher sensitivity than X-ray-KUB or US for the detection of bladder stones.	2b
Endoscopic bladder stone treatments (trans-urethral or percutaneous) are associated with comparable SFRs, but a shorter length of hospital stay, duration of procedure and duration of catheterisation compared to open cystolithotomy in adults.	1a
Stone-free rates are lower in patients treated with SWL than those treated with open or endoscopic procedures in both adults and children.	2a
Transurethral cystolithotripsy is associated with a shorter length of hospital stay, less pain and a shorter convalescence period than percutaneous cystolithotripsy in adults.	1b
Transurethral cystolithotripsy with a nephroscope is quicker than when using a cystoscope with no difference in SFR in adults.	1a
Transurethral cystolithotripsy with a resectoscope is quicker than when using a cystoscope with no difference in SFR in adults.	2a
Mechanical, pneumatic and laser appear equivalent lithotripsy modalities for use in endoscopic bladder stone treatments in adults and children.	2a
Open cystolithotomy without a retropubic drain or urethral catheter ("tubeless") is associated with a shorter length of hospital stay than traditional cystolithotomy and can be performed safely in children with primary stones and no prior bladder surgery or infections.	2b
Bladder stone removal with concomitant treatment for BOO is associated with no significant difference in major post-operative complications when compared to BOO treatment alone in adults. However, concomitant bladder stone treatment does increase the rates of short-term post-operative incontinence and UTI.	2b

The incidence of bladder stone formation in spinal cord injury patients is 15-36% after eight to ten years. The absolute annual risk of stone formation in spinal cord injury patients is significantly higher with an indwelling catheter compared to those voiding with CISC or spontaneously.	2b
The incidence of bladder stone formation after bladder augmentation or vesico-entero-cystostomy is between 2-53% in adults and children.	2b
Urinary diversion including orthotopic ileal neobladders, ileocaecal continent cutaneous urinary diversion and rectosigmoid reservoirs is associated with urinary reservoir stone formation in 0-43%.	2b
The risk of bladder stone formation in spinal cord injury, bladder augmentation or continent urinary diversion patients is reduced by performing regular bladder irrigation.	2b

Recommendations	**Strength rating**
Use ultrasound (US) as first-line imaging with symptoms suggestive of a bladder stone.	Strong
Use cystoscopy or computed tomography (CT), or kidney-ureter-bladder X-Ray (KUB) to investigate adults with persistent symptoms suggestive of a bladder stone if US is negative.	Strong
Use X-Ray KUB for adults with confirmed bladder stones to guide treatment options and follow-up.	Weak
All patients with bladder stones should be examined and investigated for the cause of bladder stone formation, including: • uroflowmetry and post-void residual; • urine dipstick, pH, ± culture; • metabolic assessment and stone analysis (see sections 3.3.2.3 and 4.1 for further details). In selected patients, consider: • upper tract imaging (in patients with a history of urolithiasis or loin pain); • cysto-urethroscopy or urethrogram.	Weak
Offer oral chemolitholysis for radiolucent or known uric acid bladder stones in adults.	Weak
Offer adults with bladder stones transurethral cystolithotripsy where possible.	Strong
Perform transurethral cystolithotripsy with a continuous flow instrument in adults (e.g., nephroscope or resectoscope) where possible.	Weak
Offer adults percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or advisable.	Strong
Suggest open cystolithotomy as an option for very large bladder stones in adults and children.	Weak
Offer children with bladder stones transurethral cystolithotripsy where possible.	Weak
Offer children percutaneous cystolithotripsy where transurethral cystolithotripsy is not possible or is associated with a high risk of urethral stricture (e.g., young children, previous urethral reconstruction, and spinal cord injury).	Weak
Open, laparoscopic, and extracorporeal shock wave lithotripsy are alternative treatments where endoscopic treatment is not advisable in adults and children.	Weak
Prefer “tubeless” procedure (without placing a catheter or drain) for children with primary bladder stones and no prior infection, surgery, or bladder dysfunction where open cystolithotomy is indicated.	Weak
Perform procedures for the stone and underlying bladder outlet obstruction (BOO) simultaneously in adults with bladder stones secondary to BOO, where possible.	Strong
Individualise imaging follow up for each patient as there is a paucity of evidence. Factors affecting follow up will include: • whether the underlying functional predisposition to stone formation can be treated (e.g., transurethral resection of the prostate [TURP]); • metabolic risk.	Weak
Recommend regular irrigation therapy with saline solution to adults and children with bladder augmentation, continent cutaneous urinary reservoir or neuropathic bladder dysfunction, and no history of autonomic dysreflexia, to reduce the risk of stone recurrence.	Weak

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8. CONFLICT OF INTEREST

All members of the Urolithiasis Guidelines working panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is available on the European Association of Urology website: http://uroweb.org/guideline/urolithiasis/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Urological Infections Guidelines Panel has compiled these clinical guidelines to provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urinary tract infections (UTIs) and male accessory gland infections. These guidelines also aim to address the important public health aspects of infection control and antimicrobial stewardship. Separate EAU guidelines documents are available addressing paediatric urological infections [1] and infections in patients with neurological urinary tract dysfunction [2].

It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Infections Guidelines Panel consists of a multi-disciplinary group of urologists, with particular expertise in this area, an infectious disease specialist and a clinical microbiologist. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions, which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://uroweb.org/guideline/urological-infections/.

1.4 Publication history

The Urological Infections Guidelines were first published in 2001. This 2022 document presents a limited update of the 2021 publication.

2. METHODS

2.1 Introduction

For the 2022 Urological Infections Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for sections 3.5 Recurrent UTI, 3.12 Acute Infective Epididymitis and 3.15 Peri-Procedural Antibiotic Prophylaxis. Broad and comprehensive literature searches, covering these sections were performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries. The time frames covered and the number of unique records identified, retrieved and screened for relevance for each section were:

Section	No. of unique records	Search time frame
3.5 Recurrent UTI	3,583	No limit cut-off 31st May 2021
3.12 Acute Infective Epididymitis	263	Jan 2017 – 31st May 2021
3.15 Peri-Procedural Antibiotic Prophylaxis	927	Jan 2017 – 31st May 2021

Detailed search strategies are available online: http://uroweb.org/guideline/urological-infections/?type=appendices-publications.

The 2022 edition of the EAU Guidelines uses a modified GRADE methodology [3]. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [4];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [5]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and on the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

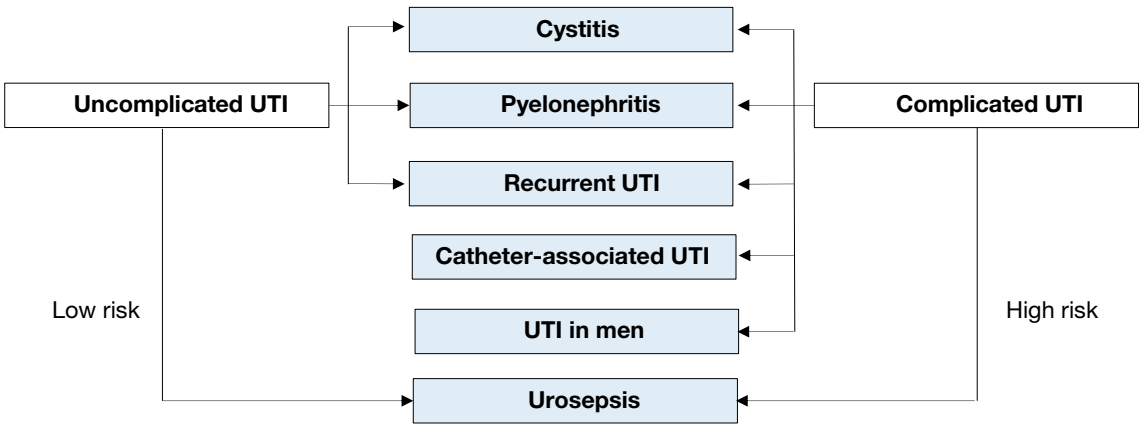
This document was subject to independent peer review prior to publication in 2019.

3. THE GUIDELINE

3.1 Classification

Different classification systems of UTI exist. Most widely used are those developed by the Centres for Disease Control and Prevention (CDC) [6], Infectious Diseases Society of America (IDSA) [7], European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [8] as well as the U.S. Food and Drug Administration (FDA) [9, 10]. Current UTI guidelines frequently use the concept of uncomplicated and complicated UTI with a number of modifications (Figure 1). In 2011 the EAU Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation of the UTI, the anatomical level of the UTI, the grade of severity of the infection, the categorisation of risk factors and availability of appropriate antimicrobial therapy [11].

Figure 1: Concept of uncomplicated and complicated UTI



The following classification of UTIs is adopted in the EAU Urological Infections Guidelines:

Classification of UTI	
Uncomplicated UTIs	Acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI, limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.
Complicated UTIs	All UTIs which are not defined as uncomplicated. Meaning in a narrower sense UTIs in a patient with an increased chance of a complicated course: i.e. all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, indwelling urinary catheters, renal diseases, and/or with other concomitant immunocompromising diseases for example, diabetes.
Recurrent UTIs	Recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months.
Catheter-associated UTIs	Catheter-associated urinary tract infection (CA-UTI) refers to UTIs occurring in a person whose urinary tract is currently catheterised or has had a catheter in place within the past 48 hours.
Urosepsis	Urosepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs [12].

3.2 Antimicrobial Stewardship

Although the benefits to patients of antibiotic use are clear, overuse and misuse have contributed to the growing problem of resistance amongst uropathogenic bacteria, which is a serious threat to public health [13, 14]. In acute care hospitals, 20-50% of prescribed antibiotics are either unnecessary or inappropriate [15]. In response, a worldwide initiative seeks to incorporate Antimicrobial Stewardship programs in healthcare [16]. Antimicrobial Stewardship aims to optimise clinical outcomes and ensure cost-effective therapy whilst minimising unintended consequences of antimicrobial use such as healthcare associated infections including *Clostridium difficile*, toxicity, selection of virulent organisms and emergence of resistant bacterial strains [17].

Stewardship programs have two main sets of actions. The first set mandates use of recommended care at the patient level conforming to guidelines. The second set describes strategies to achieve adherence to the mandated guidance. These include persuasive actions such as education and feedback together with restricting availability linked to local formularies. A Cochrane review of effectiveness of interventions to improve antibiotic prescribing practices for hospital inpatients, updated in 2017, found high-certainty evidence that such interventions are effective in increasing adherence with antibiotic policy leading to reduced antibiotic treatment duration and that it may also reduce hospital stay. The review found no evidence that reduced antibiotic usage increased mortality [18].

The important components of antimicrobial stewardship programs are [19]:

- regular training of staff in best use of antimicrobial agents;
- adherence to local, national or international guidelines;
- regular ward visits and consultation with infectious diseases physicians and clinical microbiologists;
- audit of adherence and treatment outcomes;
- regular monitoring and feedback to prescribers of their performance and local pathogen resistance profiles.

A 2016 systematic review of evidence for effectiveness of various Antimicrobial Stewardship interventions in healthcare institutions identified 145 studies of nine Stewardship objectives. Guideline-driven empirical therapy using a restricted choice of antibiotics and including de-escalation, intravenous to oral switch, therapeutic drug monitoring, and bedside consultation resulted in a 35% (95% CI 20-46%) relative risk reduction (RRR) in mortality. Use of de-escalation (tailoring to a more narrow spectrum agent), showed a RRR of 56% (95% CI 34 – 70%) for mortality [20].

To facilitate local initiatives and audit, a set of valid, reliable, and applicable indicators of the quality of antibiotic use in the treatment of hospitalised patients with complicated UTI was developed [21]. Its use in the Netherlands appeared to result in shortened hospital stay [22]. A literature search of Pubmed from April 2014 [20], to February 2017 identified no further randomised controlled trials (RCTs) relating to stewardship

programmes for UTIs. Studies to provide high-quality evidence of effectiveness of Stewardship programmes in urology patients are urgently needed.

3.3 Asymptomatic bacteriuria in adults

3.3.1 Background

Urinary growth of bacteria in an asymptomatic individual (asymptomatic bacteriuria - ABU) is common, and corresponds to a commensal colonisation [23]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [24, 25]. The aim of this section is to support the clinician in deciding when ABU should or should not be treated.

3.3.2 Epidemiology, aetiology and pathophysiology

Asymptomatic bacteriuria occurs in an estimated 1-5% of healthy pre-menopausal females. Increasing to 4-19% in otherwise healthy elderly females and men, 0.7-27% in patients with diabetes, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and in 23-89% in patients with spinal cord injuries [26]. Asymptomatic bacteriuria in younger men is uncommon, but when detected, chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence of risk factors (see sections 3.4 and 3.7).

3.3.3 Diagnostic evaluation

Asymptomatic bacteriuria in an individual without urinary tract symptoms is defined by a mid-stream sample of urine showing bacterial growth $\geq 10^5$ cfu/mL in two consecutive samples in women [27] and in one single sample in men [28]. In a single catheterised sample, bacterial growth may be as low as 10^2 cfu/mL to be considered representing true bacteriuria in both men and women [26, 29]. Cystoscopy and/or imaging of the upper urinary tract is not mandatory if the medical history is otherwise without remark. If persistent growth of urease producing bacteria, i.e. *Proteus mirabilis* is detected, stone formation in the urinary tract must be excluded [30]. In men, a digital rectal examination (DRE) has to be performed to investigate the possibility of prostate diseases (see section 3.11).

3.3.4 Evidence summary

A systematic search of the literature from January 2000 to November 2016 identified 3,582 titles of which 224 were selected for full text review and 50 were included [31]. For the subgroups of pregnancy, prior to urologic surgeries, post-menopausal women and institutionalised elderly patients only data from RCTs were included, on which a meta-analysis was performed [31]. For the other subgroups non-RCTs were also included in the narrative analysis [31]. The following patient populations were not covered by the systematic review: immuno-compromised patients; patients with candiduria; patients with dysfunctional and/or reconstructed lower urinary tracts; and patients with indwelling catheters. For these groups the guideline was updated using a structured literature search. The evidence question addressed was: What is the most effective management for people with asymptomatic bacteriuria?

3.3.5 Disease management

3.3.5.1 Patients without identified risk factors

Asymptomatic bacteriuria does not cause renal disease or damage [32]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [33], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven to be unnecessary in most high-risk patient subgroups, there is panel consensus that the results of these subgroups can also be applied to patients without identified risk factors. Therefore, screening and treatment of ABU is not recommended in patients without risk factors.

3.3.5.2 Patients with ABU and recurrent UTI, otherwise healthy

One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI without identified risk factors [25] and demonstrated that treatment of ABU increases the risk for a subsequent symptomatic UTI episode, compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; n=673). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI; therefore, treatment of ABU is not recommended.

3.3.5.3 Pregnant women

3.3.5.3.1 Is treatment of ABU beneficial in pregnant women?

Twelve RCTs comparing antibiotic treatments of ABU with placebo controls or no treatment [34-45], with different antibiotic doses and regimens were identified, ten published before 1988 and one in 2015. Eleven RCTs (n=2,002) reported on the rate of symptomatic UTIs [34, 36-44, 46]. Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment (average RR 0.22, 95% CI 0.12 to 0.40).

Six RCTs reported on the resolution of bacteriuria [34-36, 38, 41, 43]. Antibiotic treatment was effective in the resolution of bacteriuria compared to placebo (average RR 2.99, 95% CI 1.65 to 5.39; n=716). Eight RCTs reported on the rate of low birthweights [34, 36-39, 42, 45, 46]. Antibiotic treatment was associated with lower rates of low birthweight compared to placebo or no treatment (average RR 0.58, 95% CI 0.36 to 0.94; n=1,689). Four RCTs reported on the rate of preterm deliveries [42, 43, 45, 46]. Antibiotic treatment was associated with lower rates of preterm delivery compared to placebo or no treatment (average RR 0.34, 95% CI 0.18 to 0.66; n=854).

Based on the beneficial maternal and foetal effects of antibiotic treatment pregnant women should be screened and treated for ABU. However, the panel would like to emphasise that most available studies have low methodological quality and are from the 60s to 80s. Diagnostic and treatment protocols and accessibility to medical services have dramatically changed since then; therefore, the quality of evidence for this recommendation is low. In a newer study of higher methodological quality the beneficial effects of antibiotic treatment are not as evident [46]. Therefore, it is advisable to consult national recommendations for pregnant women.

3.3.5.3.2 Which treatment duration should be applied to treat ABU in pregnancy?

Sixteen RCTs comparing the efficacy of different antibiotic treatments in pregnant women with ABU were identified [47-62]. There was significant heterogeneity amongst the studies. Studies compared different antibiotic regimens or the same antibiotic regimens with different durations. The duration of treatment ranged from single dose to continuous treatment (until delivery). For practical purposes the grouping strategy used by the previously published Cochrane review by Widmer *et al*., was adopted with some modifications [63]. The following treatment groups were used for comparison:

1. single dose (single day);
2. short course (2-7 days);
3. long course (8-14 days);
4. continuous (until delivery).

Nine studies compared single dose to short course treatment [48, 52, 53, 57-62], one study compared single dose to long course treatment [56] and one study compared long course to continuous treatment [49]. As long term and continuous antibiotic treatment is not used in current practice, only studies comparing single dose to standard short course treatment are presented.

3.3.5.3.2.1 Single dose vs. short course treatment

Three RCTs reported on the rate of symptomatic UTIs [52, 61, 62], with no significant difference between the two durations (average RR 1.07, 95% CI 0.47 to 2.47; n=891). Nine RCTs reported on the rate of ABU resolution [48, 52, 53, 57-62], with no significant difference between the two durations (average RR 0.97, 95% CI 0.89 to 1.07; n=1,268). Six RCTs reported on the rate of side effects [48, 52, 57, 58, 60, 61]. Single dose treatment was associated with significantly less side effects compared to short course treatment (average RR 0.40, 95% CI 0.22 to 0.72; n=458). Three RCTs reported on the rate of preterm deliveries [52, 54, 62], with no significant difference between the two durations (average RR 1.16, 95% CI 0.75 to 1.78; n=814). One RCT reported on the rate of low birthweights [62]. There were significantly more babies with low birthweight in the single dose duration compared to short course treatment (average RR 1.65, 95% CI 1.06 to 2.57; n=714).

According to the data analysis, single dose treatment was associated with a significantly lower rate of side effects but a significantly higher rate of low birthweight. Therefore, standard short course treatment should be applied to treat ABU in pregnancy; however, it should be emphasised that the overall quality of the scientific evidence underpinning this recommendation is low.

3.3.5.4 Patients with identified risk-factors

3.3.5.4.1 Diabetes mellitus

Diabetes mellitus, even when well regulated, is reported to correlate to a higher frequency of ABU [64]. One RCT demonstrated that eradicating ABU did not reduce the risk of symptomatic UTI and infectious complications in patients with diabetes mellitus. The time to first symptomatic episode was also similar in both

groups. Furthermore, untreated ABU did not correlate to diabetic nephropathy [65]. Screening and treatment of ABU in well-controlled diabetes mellitus is therefore not recommended. However, poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications.

3.3.5.4.2 ABU in post-menopausal women

Elderly women have an increased incidence of ABU [66]. Four RCTs compared antibiotic treatment of ABU with placebo controls or no treatment, in a post-menopausal female population, with different antibiotic doses and regimens [67-70]. Women in these studies were mostly nursing home residents, which may bias the results of this analysis. Three RCTs reported on the rate of symptomatic UTIs (average RR 0.71, 95% CI 0.49 to 1.05; n=208) and the resolution of bacteriuria (average RR 1.28, 95% CI 0.50 to 3.24; n=203) [52, 61, 62], with no significant benefit of antibiotic treatment. Therefore, ABU in post-menopausal women does not require treatment, and should be managed as for pre-menopausal women.

3.3.5.4.3 Elderly institutionalised patients

The rate of ABU is 15-50% in elderly institutionalised patients [71]. Differential diagnosis of ABU from symptomatic UTI is difficult in the multi-diseased and mentally deteriorated patient, and is probably a cause of unnecessary antibiotic treatment [72, 73]. Seven RCTs compared antibiotic treatment of ABU with placebo controls or no treatment in elderly patients, with different antibiotic doses and regimens [67-70, 74-76].

Three RCTs reported on the rate of symptomatic UTIs [67, 69, 74]. Antibiotic treatment was not significantly beneficial in reducing the rate of symptomatic UTIs compared to placebo or no treatment (average RR 0.68, 95% CI 0.46 to 1.00; n=210). Six RCTs reported on the resolution of bacteriuria [67, 69, 70, 74-76]. There was no benefit of antibiotic treatment compared to placebo in the resolution of ABU (average RR 1.33, 95% CI 0.63 to 2.79; n=328). One RCT compared the rates of incontinence in this patient group before and after the eradication of ABU, and found no effect of antibiotic treatment [77]. Therefore, screening and treatment of ABU is not recommended in this patient group.

3.3.5.4.4 Patients with renal transplants

Two RCTs and two retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients [78-81]. Meta-analysis of the two RCTs did not find antibiotic treatment beneficial in terms of reducing symptomatic UTIs (RR 0.86, 95% CI 0.51 to 1.45; n=200). The two retrospective studies reached the same conclusion. Furthermore, there were no significant differences in the rate of ABU clearance, graft loss or change in renal function during long-term follow-up up to 24 months [78-81]. Therefore, treatment of ABU is not recommended in renal transplant recipients.

3.3.5.4.5 Patients with dysfunctional and/or reconstructed lower urinary tracts

Patients with lower urinary tract dysfunction (LUTD) (e.g. neurogenic bladder patients secondary to multiple sclerosis, spinal cord injury patients, patients with incomplete bladder emptying, patients with neo-bladder and ileo-cystoplasty, patients using clean intermittent catheterisation (CIC), and patients with ileal conduits, orthotopic bladder replacement and continent reservoirs) frequently become colonised [82, 83]. Studies have shown no benefit in ABU treatment in these patient groups [84, 85]. Furthermore, in LUTD patients who do not spontaneously develop ABU, deliberate colonisation with an ABU strain (*Escherichia coli* 83972) has shown a protective effect against symptomatic recurrences [84, 85]. Screening and treatment of ABU in these patient groups is therefore, not recommended. If these patient groups develop recurrent symptomatic UTI (see section 3.5) the potential protective effect of a spontaneously developed ABU against lower UTI must be considered before any treatment.

3.3.5.4.6 Patients with catheters in the urinary tract

Patients with indwelling or suprapubic catheters and nephrostomy tubes invariably become carriers of ABU, with antibiotic treatment showing no benefit [86]. This is also applicable for patients with ABU and indwelling ureteral stents [87]. Routine treatment of catheter-associated bacteriuria is not recommended. For detailed recommendations see section 3.8.

3.3.5.4.7 Patients with ABU subjected to catheter placements/exchanges

In patients subjected to uncomplicated placement/exchanges of indwelling urethral catheters ABU is not considered a risk factor and should not be screened or treated [88]. In patients subjected to placement/exchanges of nephrostomy tubes and indwelling ureteral stents, ABU is considered a risk factor for infectious complications [89]; therefore, screening and treatment prior to the procedure is recommended.

3.3.5.4.8 Immuno-compromised and severely diseased patients, patients with candiduria

These patient groups have to be considered individually and the benefit of screening and treatment of ABU should be reviewed in each case. Patients with asymptomatic candiduria may, although not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended [90].

3.3.5.5 Prior to urological surgery

In diagnostic and therapeutic procedures not entering the urinary tract, ABU is generally not considered as a risk factor, and screening and treatment are not considered necessary. On the other hand, in procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor.

Two RCTs [91, 92] and two prospective non-randomised studies [93, 94] compared the effect of antibiotic treatment to no treatment before transurethral prostate or bladder tumour resections. Antibiotic treatment significantly reduced the number of post-operative symptomatic UTIs compared to no treatment in the meta-analysis of the two RCTs (average RR 0.20, 95% CI 0.05 to 0.86; n=167). The rates of post-operative fever and septicaemia were also significantly lower in case of antibiotic treatment compared to no treatment in the two RCTs. One RCT including patients with spinal cord injury undergoing elective endoscopic urological surgeries found no significant difference in the rate of post-operative UTIs between single-dose or three to five days short term pre-operative antibiotic treatment of ABU [95].

A urine culture must therefore be taken prior to such interventions and in case of ABU, pre-operative treatment is recommended.

3.3.5.6 Prior to orthopaedic surgery

One RCT (n=471) and one multicentre cohort study (n=303) comparing the treatment of ABU with no treatment prior to orthopaedic surgery (hip arthroplasty/hemiarthroplasty or total knee arthroplasty) were identified [96, 97]. Neither of the studies showed a beneficial effect of antibiotic treatment in terms of prosthetic joint infection (3.8% vs. 0% and 3.9% vs. 4.7%, respectively). The cohort study reported no significant difference in the rate of post-operative symptomatic UTI (0.65% vs. 2.7%) [97]. Therefore, treatment of bacteriuria is not recommended prior to arthroplasty surgery.

3.3.5.7 Pharmacological management

If the decision is taken to eradicate ABU, the same choice of antibiotics and treatment duration as in symptomatic uncomplicated (section 3.4.4.4) or complicated (section 3.7.5) UTI can be given, depending on gender, medical background and presence of complicating factors. Treatment should be tailored and not empirical.

*3.3.6 **Follow-up***

There are no studies focusing on follow-up after treatment of ABU.

*3.3.7 **Summary of evidence and recommendations for the management of ABU***

Summary of evidence	**LE**
Treatment of asymptomatic bacteriuria is not beneficial in the following conditions:	
• women without risk factors;	3b
• patients with well-regulated diabetes mellitus;	1b
• post-menopausal women;	1a
• elderly institutionalised patients;	1a
• patients with dysfunctional and/or reconstructed lower urinary tracts;	2b
• patients with renal transplants;	1a
• patients prior to arthroplasty surgeries.	1b
Treatment of asymptomatic bacteriuria is harmful in patients with recurrent urinary tract infections.	1b
Treatment of asymptomatic bacteriuria is beneficial prior to urological procedures breaching the mucosa.	1a
Treatment of asymptomatic bacteriuria in pregnant women was found to be beneficial by meta-analysis of the available evidence; however, most studies are old. A recent study reported lower rates of pyelonephritis in low-risk women.	1a

Recommendations	Strength rating
Do not screen or treat asymptomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with renal transplants; • patients prior to arthroplasty surgeries; • patients with recurrent urinary tract infections.	Strong
Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa.	Strong
Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment.	Weak

3.4 Uncomplicated cystitis

*3.4.1 **Introduction***

Uncomplicated cystitis is defined as acute, sporadic or recurrent cystitis limited to non-pregnant women with no known relevant anatomical and functional abnormalities within the urinary tract or comorbidities.

*3.4.2 **Epidemiology, aetiology and pathophysiology***

Almost half of all women will experience at least one episode of cystitis during their lifetime. Nearly one in three women will have had at least one episode of cystitis by the age of 24 years [98]. Risk factors include sexual intercourse, use of spermicides, a new sexual partner, a mother with a history of UTI and a history of UTI during childhood. The majority of cases of uncomplicated cystitis are caused by *E. coli*.

*3.4.3 **Diagnostic evaluation***

3.4.3.1 Clinical diagnosis

The diagnosis of uncomplicated cystitis can be made with a high probability based on a focused history of lower urinary tract symptoms (dysuria, frequency and urgency) and the absence of vaginal discharge [99, 100]. In elderly women genitourinary symptoms are not necessarily related to cystitis [101, 102].

3.4.3.2 Differential diagnosis

Uncomplicated cystitis should be differentiated from ABU, which is considered not to be infection but rather a commensal colonisation, which should not be treated and therefore not screened for, except if it is considered a risk factor in clearly defined situations (see section 3.3).

3.4.3.3 Laboratory diagnosis

In patients presenting with typical symptoms of an uncomplicated cystitis urine analysis (i.e. urine culture, dip stick testing, etc.) leads only to a minimal increase in diagnostic accuracy [103]. However, if the diagnosis is unclear dipstick analysis can increase the likelihood of an uncomplicated cystitis diagnosis [104, 105]. Taking a urine culture is recommended in patients with atypical symptoms, as well as those who fail to respond to appropriate antimicrobial therapy [106, 107].

3.4.3.4 Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis

Summary of evidence	LE
An accurate diagnosis of uncomplicated cystitis can be based on a focused history of lower urinary tract symptoms and the absence of vaginal discharge or irritation.	2b

Recommendations	Strength rating
Diagnose uncomplicated cystitis in women who have no other risk factors for complicated urinary tract infections based on: • a focused history of lower urinary tract symptoms (dysuria, frequency and urgency); • the absence of vaginal discharge.	Strong
Use urine dipstick testing for diagnosis of acute uncomplicated cystitis.	Weak
Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within four weeks after completion of treatment; • women who present with atypical symptoms; • pregnant women.	Strong

*3.4.4 **Disease management***

Antimicrobial therapy is recommended because clinical success is significantly more likely in women treated with antimicrobials compared with placebo [108]. In female patients with mild-to-moderate symptoms, symptomatic therapy (e.g. Ibuprofen), as an alternative to antimicrobial treatment, may be considered in consultation with individual patients [109-112]. The choice of antimicrobial therapy should be guided by [99]:

- spectrum and susceptibility patterns of the aetiological pathogens;
- efficacy for the particular indication in clinical studies;
- tolerability and adverse reactions;
- adverse ecological effects;
- costs;
- availability.

According to these principles and the available susceptibility patterns in Europe, oral treatment with fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg three times a day for three to five days, and nitrofurantoin (e.g. nitrofurantoin monohydrate/macrocrystals 100 mg twice daily for five days), should be considered for first-line treatment, when available [113-116].

Alternative antimicrobials include trimethoprim alone or combined with a sulphonamide. Co-trimoxazole (160/800 mg twice daily for three days) or trimethoprim (200 mg twice daily for five days) should only be considered as drugs of first choice in areas with known resistance rates for *E. coli* of < 20% [117, 118].

Aminopenicillins are no longer suitable for empirical therapy because of worldwide high *E. coli* resistance. Aminopenicillins in combination with a beta-lactamase inhibitor such as ampicillin/sulbactam or amoxicillin/clavulanic acid and oral cephalosporins are not recommended for empirical therapy due to ecological collateral damage, but may be used in selected cases [119, 120].

Important notice:

On March 11, 2019 the European Commission implemented stringent regulatory conditions regarding the use of fluoroquinolones due to their disabling and potentially long-lasting side effects [121]. This legally binding decision is applicable in all EU countries. National authorities have been urged to enforce this ruling and to take all appropriate measures to promote the correct use of this class of antibiotics. In uncomplicated cystitis a fluoroquinolone should only be used when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections [121].

3.4.4.1 Cystitis in pregnancy

Short courses of antimicrobial therapy can also be considered for treatment of cystitis in pregnancy [122], but not all antimicrobials are suitable during pregnancy. In general, penicillins, cephalosporins, fosfomycin, nitrofurantoin (not in case of glucose-6-phosphate dehydrogenase deficiency and during the end of pregnancy), trimethoprim (not in the first trimenon) and sulphonamides (not in the last trimenon), can be considered.

3.4.4.2 Cystitis in men

Cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection. Therefore, treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI. A treatment duration of at least seven days is recommended, preferably with trimethoprim sulfamethoxazole or a fluoroquinolone if in accordance with susceptibility testing (see section 3.4.4.4) [123].

3.4.4.3 Renal insufficiency

In patients with renal insufficiency the choice of antimicrobials may be influenced by decreased renal excretion; however, most antimicrobials, have a wide therapeutic index. No adjustment of dose is necessary until glomerular filtration rate (GFR) is < 20 mL/min, with the exception of antimicrobials with nephrotoxic potential, e.g. aminoglycosides. The combination of loop diuretics (e.g. furosemide) and a cephalosporin is nephrotoxic. Nitrofurantoin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m^2 as accumulation of the drug leads to increased side effects as well as reduced urinary tract recovery, with the risk of treatment failure [124].

3.4.4.4 Summary of evidence and recommendations for antimicrobial therapy for uncomplicated cystitis

Summary of evidence	**LE**
Clinical success for the treatment of uncomplicated cystitis is significantly more likely in women treated with antimicrobials than placebo.	1b
Aminopenicillins are no longer suitable for antimicrobial therapy in uncomplicated cystitis because of negative ecological effects, high resistance rates and their increased selection for extended spectrum beta-lactamase (ESBL)-producing bacteria.	3

Recommendations	**Strength rating**
Prescribe fosfomycin trometamol, pivmecillinam or nitrofurantoin as first-line treatment for uncomplicated cystitis in women.	Strong
Do not use aminopenicillins or fluoroquinolones to treat uncomplicated cystitis.	Strong

Table 1: Suggested regimens for antimicrobial therapy in uncomplicated cystitis

Antimicrobial	**Daily dose**	**Duration of therapy**	**Comments**
First-line women			
Fosfomycin trometamol	3 g SD	1 day	Recommended only in women with uncomplicated cystitis.
Nitrofurantoin macrocrystal	50-100 mg four times a day	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg b.i.d	5 days	
Nitrofurantoin macrocrystal prolonged release	100 mg b.i.d	5 days	
Pivmecillinam	400 mg t.i.d	3-5 days	
Alternatives			
Cephalosporins (e.g. cefadroxil)	500 mg b.i.d	3 days	Or comparable
If the local resistance pattern for E. coli is < 20%			
Trimethoprim	200 mg b.i.d	5 days	Not in the first trimenon of pregnancy
Trimethoprim-sulfamethoxazole	160/800 mg b.i.d	3 days	Not in the last trimenon of pregnancy
Treatment in men			
Trimethoprim-sulfamethoxazole	160/800 mg b.i.d	7 days	Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.

SD = single dose; b.i.d = twice daily; t.i.d = three times daily.

*3.4.5 **Follow-up***

Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated [26]. In women whose symptoms do not resolve by end of treatment, and in those whose symptoms resolve but recur within two weeks, urine culture and antimicrobial susceptibility testing should be performed [125]. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used. Retreatment with a seven-day regimen using another agent should be considered [125].

3.5 Recurrent UTIs

*3.5.1 **Introduction***

Recurrent UTIs (rUTIs) are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated aetiology.

*3.5.2 **Diagnostic evaluation***

Recurrent UTIs are common. Risk factors are outlined in Table 2. Diagnosis of rUTI should be confirmed by urine culture. An extensive routine workup including cystoscopy, imaging, etc., is not routinely recommended as the diagnostic yield is low [126]. However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or urothelial cancer is suspected.

Table 2: Age-related associations of rUTI in women [71, 101, 127]

Young and pre-menopausal women	Post-menopausal and elderly women
Sexual intercourse	History of UTI before menopause
Use of spermicide	Urinary incontinence
A new sexual partner	Atrophic vaginitis due to oestrogen deficiency
A mother with a history of UTI	Cystocele
History of UTI during childhood	Increased post-void urine volume
Blood group antigen secretory status	Blood group antigen secretory status
	Urine catheterisation and functional status deterioration in elderly institutionalised women

*3.5.3 **Disease management and follow-up***

Prevention of rUTIs includes counselling regarding avoidance of risk factors, non-antimicrobial measures and antimicrobial prophylaxis [125]. These interventions should be attempted in this order. Any urological risk factor must be identified and treated. Significant residual urine should be treated optimally, including by clean intermittent catheterisation (CIC) when judged to be appropriate.

3.5.3.1 Evidence Summary

A broad literature search with cut-off of May 31st, 2021 identified 3,604 abstracts of which 361 were selected for full text review. In total 114 systematic reviews or guidelines based on systematic literature searches and 131 original publications were selected for further analysis. A further eighteen relevant publications were identified from the references of the reviewed studies. Selected studies were assigned to one of nine subgroups based on the method of prevention. The evidence question addressed was: In women with recurrent symptomatic lower UTI what interventions reduce the rate of recurrence?

3.5.3.2 Behavioural modifications

Women with rUTI should be counselled on avoidance of risks (eg, insufficient hydration, habitual and post-coital delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear) before initiation of long-term prophylactic drug treatment, although there is limited evidence available regarding these approaches [128, 129]. A open-label RCT found that additional fluid intake of 1.5 L in pre-menopausal women with rUTI who were low-volume drinkers (< 1.5 L a day) reduced the number of cystitis episodes and antibiotic usage over a twelve-month period [130]

3.5.3.3 Non-antimicrobial prophylaxis

3.5.3.3.1 Hormonal replacement

Based on the results of four meta-analyses topical oestrogen admission (either as a creme or a pessary) shows a trend towards rUTI prevention [131-134]. All studies reported that application was superior compared to placebo but was inferior compared to antibiotics. Due to its pharmacokinetics vaginal admission has no systematic side effects, however local irritation and minor bleeding can occur. The use of oral oestrogens was not effective for rUTI prophylaxis compared to placebo, furthermore it was associated with an unfavourable systematic side effect profile. A single prospective, non-comparative study of 30 pre-menopausal women with rUTI on oral contraceptives reported a beneficial effect of topical oestrogen admission [135].

3.5.3.3.2 Immunoactive prophylaxis

Several meta-analyses and systematic reviews based on nine RCTs showed that oral immunotherapy with

OM-89 is an effective and safe method for the prevention of rUTIs compared to placebo at short-term follow-up (< six months) [132, 136, 137]. A vaginal suppository containing ten strains of heat-killed uropathogenic bacteria significantly reduced the risk of rUTI compared to placebo in a meta-analysis of three small RCTs [136-138]. The preventive effect was more pronounced with booster treatment.

3.5.3.3.3 Prophylaxis with probiotics (*Lactobacillus* spp.)

Four meta-analyses with differing results and ten relevant systematic reviews were identified [132, 139-151]. Two meta-analyses reported significant positive effects for rUTI prevention with effective probiotics compared to placebo [143, 145]. The contradictory results of the four meta-analyses are a result of the analysis of different Lactobacillus strains and different administration regimes, treatment durations, and patient populations. Most studies concluded that not all Lactobacillus strains are effective for vaginal flora restoration and rUTI prevention. The highest efficacy was shown with *L. rhamnosus* GR-1, *L. reuteri* B-54, *L. reuteri* RC-14, *L. casei shirota*, and *L. crispatus* CTV-05 [132, 141, 143, 145]. Although meta-analyses including all known Lactobacilli strains did not show a significant treatment benefit [132, 141, 143, 145], sensitivity analysis excluding studies using ineffective strains resulted in a positive treatment effect [143].

Of the ten systematic reviews seven concluded that prophylaxis with vaginal probiotics has a beneficial clinical impact for the prevention of rUI [133, 134, 139, 142, 144, 146-149, 151]. The available data was of too low-quality to allow the panel to make recommendations on the route of admission, optimal dosage, and treatment duration for probiotic prophylaxis.

3.5.3.3.4 Prophylaxis with cranberry

Six meta-analyses and several systematic reviews including 82 clinical trials were identified [132, 152-156]. A Cochrane review and meta-analysis found that when compared with placebo, water or no treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI overall or in women with recurrent UTIs [152]. However, five subsequent meta-analyses concluded that consumption of cranberry-containing products may protect against UTIs in certain patient populations [132, 153-156]. The differing outcomes across the meta-analyses can be contributed to the clinical and methodological heterogeneity of the included studies [157]. Although the efficacy of cranberry products is unclear, the panel consensus is that clinicians may recommend them for rUTI prevention in women who are informed of the weak evidence base due to their favourable benefit to harm ratio. However, there is no clear clinical evidence regarding the appropriate dose and treatment duration.

3.5.3.3.5 Prophylaxis with D-mannose

A meta-analysis including one RCT, one randomised cross-over trial and one prospective cohort study analysed data on 390 patients and found that D-mannose was effective for rUTI prevention compared to placebo with comparable efficacy to antibiotic prophylaxis [158]. Another systematic review, concluded that D-mannose had a significant effect on UTI, but that further studies were needed to confirm these findings [139].

3.5.3.3.6 Endovesical instillation

Endovesical instillations of hyaluronic acid (HA) and chondroitin sulphate (CS) have been used for glycosaminoglycan (GAG) layer replenishment in the treatment of interstitial cystitis, overactive bladder, radiation cystitis, and for prevention of rUTI [159]. A meta-analysis (n=143) based on two RCTs and two non-RCTs found significantly decreased UTI rates per patient/year and significantly longer mean UTI recurrence times for HA and HA-CS therapy compared to control treatment [160]. In addition, subgroup analysis of the two RCTs using HA-CS reported a significantly decreased UTI rate per patient/year, significantly longer mean UTI recurrence time and a significantly better pelvic pain and urgency/frequency (PUF) total score. However, 24 hour urinary frequency was not significantly improved after therapy [160].

Another meta-analysis (n=800) including two RCTs and six non-RCTs found that when compared to control treatment HA, with or without CS, was associated with a significantly lower mean UTI rate per patient/year and a significantly longer time to UTI recurrence [161]. Furthermore, HA-CS therapy was associated with significantly greater mean reductions in PUF total and symptom scores and the percentage of patients with UTI recurrence during follow-up was also lower [161].

As randomised controlled studies are available only for HA plus CS, the quality of evidence is higher for the combination than for HA alone.

3.5.3.3.7 Methenamine hippurate

A Cochrane review from 2012 based on thirteen studies, with high levels of heterogeneity, concluded that methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis [162]. However, a meta-analysis from 2021 based on six studies found that although studies showed a trend towards a benefit for methenamine hippurate in prevention

of rUTIs there was no statistically significant difference between the efficacy of methenamine hippurate and any comparators [163]. Due to these contradictory results, no recommendation on the use of methenamine can be made.

3.5.3.4 Antimicrobials for preventing rUTI

3.5.3.4.1 Continuous low-dose antimicrobial prophylaxis and post-coital prophylaxis

Four meta-analyses and numerous systematic reviews and guidelines were identified [134, 164-174]. All available meta-analyses conclude that antibiotic prophylaxis is the most effective approach against UTI recurrences compared with placebo or no treatment [164-166]. Antimicrobials may be given as continuous low-dose prophylaxis for longer periods, or as post-coital prophylaxis. There is no significant difference in the efficacy of the two approaches. There is no consensus about the optimal duration of continuous antimicrobial prophylaxis, with studies reporting treatment duration of three to twelve months. After discontinuation of the drug, UTIs tend to re-occur, especially among those who have had three or more infections annually. It is mandatory to offer both continuous low-dose antimicrobial and post-coital prophylaxis after counselling, and when behavioural modifications and non-antimicrobial measures have been unsuccessful.

Differences in outcomes between antibiotics did not reach statistical significance. The choice of agent should be based on the local resistance patterns. Regimens include nitrofurantoin 50 mg or 100 mg once daily, fosfomycin trometamol 3 g every ten days, trimethoprim 100 mg once daily and during pregnancy cephalexin 125 mg or 250 mg or cefaclor 250 mg once daily [125, 175]. Post-coital prophylaxis should be considered in pregnant women with a history of frequent UTIs before onset of pregnancy, to reduce their risk of UTI [176].

3.5.3.4.2 Self-diagnosis and self-treatment

In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered [177]. The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI (section 3.4.4.4).

*3.5.4 **Summary of evidence and recommendations for the diagnostic evaluation and treatment of rUTIs***

Summary of evidence	**LE**
Extensive routine workup including cystoscopy, imaging, etc., has a low diagnostic yield for the diagnosis of rUTI.	3
Increased water intake is an effective antimicrobial-sparing strategy to prevent rUTI in pre-menopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily.	3
Vaginal oestrogen replacement has shown a trend towards preventing rUTI in post-menopausal women.	1b
Immunoactive prophylaxis has been shown to be more effective than placebo in female patients with rUTIs in several RCTs with a good safety profile.	1a
Probiotics containing *L. rhamnosus* GR-1, *L. reuteri* B-54 and RC-14, *L. casei shirota*, or *L. crispatus* CTV-05 are effective for vaginal flora restoration and prevention of rUTIs.	1b
Current scientific evidence regarding the efficacy of cranberry products in the prevention of UTIs is divided.	1a
Based on limited evidence, D-mannose can significantly reduce the number of UTI episodes and can be an effective agent for UTI prevention in selected patients.	2
Based on limited evidence intravesical GAG therapy can reduce the number of UTIs per patient per year, and prolong the time interval between rUTI episodes.	2
Both continuous low-dose antimicrobial prophylaxis and post-coital antimicrobial prophylaxis, have been shown to reduce the rate of rUTI.	1b
A prospective cohort study showed that intermittent self-start therapy is effective, safe and economical in women with rUTIs.	2b

Recommendations	**Strength rating**
Diagnose recurrent UTI by urine culture.	Strong
Do not perform an extensive routine workup (e.g cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors.	Weak
Advise pre-menopausal women regarding increased fluid intake as it might reduce the risk of recurrent UTI.	Weak
Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI.	Strong

Use immunoactive prophylaxis to reduce recurrent UTI in all age groups.	Strong
Advise patients on the use of local or oral probiotics containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs.	Weak
Advise patients on the use of cranberry products to reduce recurrent UTI episodes; however, patients should be informed that the quality of evidence underpinning this is low with contradictory findings.	Weak
Use D-mannose to reduce recurrent UTI episodes, but patients should be informed that further studies are needed to confirm the results of initial trials.	Weak
Use endovesical instillations of hyaluronic acid or a combination of hyaluronic acid and chondroitin sulphate to prevent recurrent UTIs in patients where less invasive preventive approaches have been unsuccessful. Patients should be informed that further studies are needed to confirm the results of initial trials.	Weak
Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects.	Strong
For patients with good compliance self-administered short-term antimicrobial therapy should be considered.	Strong

3.6 Uncomplicated pyelonephritis

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known relevant urological abnormalities or comorbidities.

*3.6.1 **Diagnostic evaluation***

3.6.1.1 Clinical diagnosis

Pyelonephritis is suggested by fever (> 38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis [178]. Pregnant women with acute pyelonephritis need special attention, as this kind of infection may not only have an adverse effect on the mother with anaemia, renal and respiratory insufficiency, but also on the unborn child with more frequent pre-term labour and birth [179].

3.6.1.2 Differential diagnosis

It is vital to differentiate as soon as possible between uncomplicated and complicated mostly obstructive pyelonephritis, as the latter can rapidly lead to urosepsis. This differential diagnosis should be made by the appropriate imaging technique (see section 3.6.1.4).

3.6.1.3 Laboratory diagnosis

Urinalysis including the assessment of white and red blood cells and nitrite, is recommended for routine diagnosis [180]. In addition, urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis.

3.6.1.4 Imaging diagnosis

Evaluation of the upper urinary tract with ultrasound (US) should be performed to rule out urinary tract obstruction or renal stone disease in patients with a history of urolithiasis, renal function disturbances or a high urine pH [181]. Additional investigations, such as a contrast enhanced computed tomography (CT) scan, or excretory urography should be considered if the patient remains febrile after 72 hours of treatment, or immediately if there is deterioration in clinical status [181]. For diagnosis of complicating factors in pregnant women, US or magnetic resonance imaging (MRI) should be used preferentially to avoid radiation risk to the foetus [181].

*3.6.2 **Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis***

Summary of evidence	**LE**
Urine culture and antimicrobial susceptibility testing should be performed in all cases of pyelonephritis in addition to urinalysis.	4
A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule.	2b
Additional imaging investigations, such as a contrast enhanced CT scan should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis.	4

Recommendations	Strength rating
Perform urinalysis (e.g. using the dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis.	Strong
Perform urine culture and antimicrobial susceptibility testing in patients with pyelonephritis.	Strong
Perform imaging of the urinary tract to exclude urgent urological disorders.	Strong

*3.6.3 **Disease management***

3.6.3.1 Outpatient treatment

Fluoroquinolones and cephalosporines are the only antimicrobial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis [182]. However, oral cephalosporines achieve significantly lower blood and urinary concentrations than intravenous cephalosporines. Other agents such as nitrofurantoin, oral fosfomycin, and pivmecillinam should be avoided as there is insufficient data regarding their efficacy [183]. In the setting of fluoroquinolone hypersensitivity or known resistance, other acceptable choices include trimethoprim-sulfamethoxazole (160/800 mg) or an oral beta-lactam, if the uropathogen is known to be susceptible. If such agents are used in the absence of antimicrobial susceptibility results, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered. A short outpatient antibiotic course of treatment, for acute pyelonephritis, has been shown to be equivalent to longer durations of therapy in terms of clinical and microbiological success. However, this is associated with a higher recurrence rate of infection within four to six weeks and needs to be tailored to local policies and resistance patterns [184].

3.6.3.2 Inpatient treatment

Patients with uncomplicated pyelonephritis requiring hospitalisation should be treated initially with an intravenous antimicrobial regimen e.g. a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin [185]. Ceftolozane/tazobactam achieved a clinical response rate of over 90% in patients with uncomplicated pyelonephritis [186, 187]. It also demonstrated significantly higher composite cure rates than levofloxacin among levofloxacin-resistant pathogens [188]. Ceftazidime-avibactam combination has been shown to be effective for treating ceftazidime-resistant *Enterobacterales* and *Pseudomonas aeruginosa* UTIs [189].

Novel antimicrobial agents include imipenem/cilastatin, cefiderocol, meropenem-vaborbactam and plazomicin. Imipenem/cilastatin has been investigated in a phase 2 randomised trial and showed good clinical response rates [190]. Cefatazidime-avibactam and doripenem showed similar efficacy against ceftazidime non-susceptible pathogens and may offer an alternative to carbapenems in this setting [191]. Meropenem-vaborbactam has been shown to be non-inferior to piperacillin-tazobactam in a phase 3 RCT [192]. It was also effective for treating carbapenem-resistant *Enterobacterales* with cure rates of 65% compared to best available treatment [193]. Once daily plazomicin was non-inferior to meropenem for the treatment of cUTIs and acute pyelonephritis caused by *Enterobacterales*, including multidrug-resistant strains [194]. Cefiderocol was non-inferior to imipenem/cilastatin for the treatment of complicated UTI in people with multidrug-resistant Gram-negative infections in a phase 2 RCT [195].

Carbapenems and novel broad spectrum antimicrobial agents should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms. The choice between these agents should be based on local resistance patterns and optimised on the basis of drug susceptibility results. In patients presenting with signs of urosepsis empiric antimicrobial coverage for ESBL-producing organisms is warranted [196]. Patients initially treated with parenteral therapy who improve clinically and can tolerate oral fluids may transition to oral antimicrobial therapy [197].

3.6.3.2.1 Summary of evidence and recommendations for the treatment of uncomplicated pyelonephritis

Summary of evidence	LE
Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis.	1b
Intravenous antimicrobial regimens for uncomplicated pyelonephritis may include a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin.	1b
Carbapenems should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms.	4
The appropriate antimicrobial should be chosen based on local resistance patterns and optimised on the basis of drug susceptibility results.	3

Recommendations	Strength rating
Treat patients with uncomplicated pyelonephritis not requiring hospitalisation with short course fluoroquinolones as first-line treatment.	Strong
Treat patients with uncomplicated pyelonephritis requiring hospitalisation with an intravenous antimicrobial regimen initially.	Strong
Switch patients initially treated with parenteral therapy, who improve clinically and can tolerate oral fluids, to oral antimicrobial therapy.	Strong
Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis.	Strong

Table 3: Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobial	Daily dose	Duration of therapy	Comments
Ciprofloxacin	500-750 mg b.i.d	7 days	Fluoroquinolone resistance should be less than 10%.
Levofloxacin	750 mg q.d	5 days	
Trimethoprim sulfamethoxazol	160/800 mg b.i.d	14 days	If such agents are used empirically, an initial intravenous dose of a long-acting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	
Ceftibuten	400 mg q.d	10 days	

b.i.d = twice daily; q.d = every day.

Table 4: Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobials	Daily dose	Comments
First-line treatment		
Ciprofloxacin	400 mg b.i.d	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1-2 g q.d	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1-2 g b.i.d	Lower dose studied, but higher dose recommended.
Piperacillin/tazobactam	2.5-4.5 g t.i.d	
Gentamicin	5 mg/kg q.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Amikacin	15 mg/kg q.d	
Last-line alternatives		
Imipenem/cilastatin	0.5 g t.i.d	Consider only in patients with early culture results indicating the presence of multi-drug resistant organisms.
Meropenem	1 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Cefiderocol	2 g t.i.d	
Meropenem-vaborbactam	2 g t.i.d	
Plazomicin	15 mg/kg o.d	

b.i.d = twice daily; t.i.d = three times daily; q.d = every day; o.d = once daily.

In pregnant women with pyelonephritis, outpatient management with appropriate parenteral antimicrobials may also be considered, provided symptoms are mild and close follow-up is feasible [198, 199]. In more severe cases of pyelonephritis, hospitalisation and supportive care are usually required. After clinical improvement parenteral therapy can also be switched to oral therapy for a total treatment duration of seven to ten days. In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of two weeks is recommended, preferably with a fluoroquinolone since prostatic involvement is frequent [200].

*3.6.4 **Follow-up***

Post-treatment urinalysis or urine cultures in asymptomatic patients post-therapy are not indicated.

3.7 Complicated UTIs

3.7.1 ***Introduction***

A complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection [201-203]. New insights into the management of cUTIs also suggest to consider infections caused by multi-drug resistant uropathogens [204]. The underlying factors that are generally accepted to result in a cUTI are outlined in Table 5. The designation of cUTI encompasses a wide variety of underlying conditions that result in a remarkably heterogeneous patient population. Therefore, it is readily apparent that a universal approach to the evaluation and treatment of cUTIs is not sufficient, although there are general principles of management that can be applied to the majority of patients with cUTIs. The following recommendations are based on the Stichting Werkgroep Antibioticabeleid (SWAB) Guidelines from the Dutch Working Party on Antibiotic Policy [205].

Table 5: Common factors associated with complicated UTIs [204-207]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes mellitus
Vesicoureteral reflux	Immunosuppression
Recent history of instrumentation	Healthcare-associated infections
Isolated ESBL-producing organisms	Isolated multi-drug resistant organisms

3.7.2 ***Diagnostic evaluation***

3.7.2.1 Clinical presentation

A cUTI is associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may be atypical for example, in neuropathic bladder disturbances, CA-UTI or patients who have undergone radical cystectomy with urinary diversion. In addition, all patients with nephrostomy may have an atypical clinical presentation. Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. Clinicians must also recognise that symptoms, especially lower urinary tract symptoms (LUTS), are not only caused by UTIs but also by other urological disorders, such as, for example, benign prostatic hyperplasia and autonomic dysfunction in patients with spinal lesions and neurogenic bladders. Concomitant medical conditions, such as diabetes mellitus and renal failure, which can be related to urological abnormalities, are often also present in a cUTI.

3.7.2.2 Urine culture

Laboratory urine culture is the recommended method to determine the presence or absence of clinically significant bacteriuria in patients suspected of having a cUTI.

3.7.3 ***Microbiology (spectrum and antimicrobial resistance)***

A broad range of micro-organisms cause cUTIs. The spectrum is much larger than in uncomplicated UTIs and the bacteria are more likely to be resistant (especially in treatment-related cUTI) than those isolated in uncomplicated UTIs [206, 207]. *E. coli*, *Proteus spp., Klebsiella spp., Pseudomonas spp., Serratia spp*. and *Enterococcus spp*. are the most common species found in cultures. *Enterobacterales* predominate (60-75%), with *E. coli* as the most common pathogen; particularly if the UTI is a first infection. Otherwise, the bacterial spectrum may vary over time and from one hospital to another [208].

3.7.4 ***General principles of cUTI treatment***

Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antimicrobial agent on the basis of the isolated uropathogen.

3.7.4.1 Choice of antimicrobials

Considering the current resistance percentages of amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, it can be concluded that these agents are not suitable for the empirical treatment of

pyelonephritis in a normal host and, therefore, also not for treatment of all cUTIs [209]. The same applies to ciprofloxacin and other fluoroquinolones in urological patients [209].

Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin, or a second or third generation cephalosporin, or an extended-spectrum penicillin with or without an aminoglycoside [205]. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results [183]. These recommendations are not only suitable for pyelonephritis, but for all other cUTIs.

Alternative regimens for the treatment of cUTIs, particularly those caused by multidrug-resistant pathogens have been studied. Ceftolozane/tazobactam 1.5 g every eight hours demonstrated high clinical cure rates for cUTIs caused by ESBL-producing *Enterobacterales* in a pooled analysis of phase 3 clinical trials [210]. Cefiderocol (2 g) three times daily was non-inferior to imipenem-cilastatin (1 g) three times daily for the treatment of cUTI in patients with multidrug-resistant Gram-negative infections [195]. Imipenem/cilastatin plus relebactam (250 or 125 mg) was as effective as imipenem/cilastatin alone for treatment of cUTI in a phase 2 RCT [190]. Ceftazidime/avibactam has been shown to be as effective as carbapenems for the treatment of cUTI in a systematic review reporting a baseline of 25% for ESBL-producing *Enterobacterales*, but more severe adverse events were reported in the ceftazidime/avibactam group [211]. Once-daily plazomicin was shown to be non-inferior to meropenem for the treatment of cUTIs caused by *Enterobacterales*, including multidrug-resistant strains [194].

In view of the high degree of resistance, particularly among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last six months [212]. Fluoroquinolones can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to beta-lactam antimicrobials. Intravenous levofloxacin 750 mg once daily for five days has been shown to be non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms) [213].

3.7.4.2 Duration of antimicrobial therapy

Treatment for seven [214] to fourteen days (for men fourteen days when prostatitis cannot be excluded) [215], is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality. When the patient is hemodynamically stable and afebrile for at least 48 hours, a shorter treatment duration (e.g. seven days) may be considered in patients where a short-course treatment is desired due to relative-contraindications to the administered antibiotic [213].

*3.7.5 **Summary of evidence and recommendations for the treatment of complicated UTIs***

Summary of evidence	**LE**
Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen chosen based on local resistance data and previous urine culture results from the patient, if available. The regimen should be tailored on the basis of susceptibility result.	1b
If the prevalence of fluoroquinolone resistance is thought to be < 10% and the patient has contraindications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with complicated pyelonephritis.	2
In the event of hypersensitivity to penicillin a cephalosporins can still be prescribed, unless the patient has had systemic anaphylaxis in the past.	2
In patients with a cUTI with systemic symptoms, empirical treatment should cover ESBL if there is an increased likelihood of ESBL infection based on prevalence in the community, earlier collected cultures and prior antimicrobial exposure of the patient.	2
Intravenous levofloxacin 750 mg once daily for five days, is non-inferior to a seven to fourteen day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms).	2

Recommendations	Strength rating
Use the combination of: • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms.	Strong
Only use ciprofloxacin provided that the local resistance percentages are < 10% when: • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials.	Strong
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months.	Strong
Manage any urological abnormality and/or underlying complicating factors.	Strong

3.8 Catheter-associated UTIs

*3.8.1 **Introduction***

Catheter-associated UTI refers to UTIs occurring in a person whose urinary tract is currently catheterised or has been catheterised within the past 48 hours. The urinary catheter literature is problematic as many published studies use the term CA-bacteriuria without providing information on what proportion are CA-ABU and CA-UTI, and some studies use the term CA-UTI when referring to CA-ABU or CA-bacteriuria [206].

*3.8.2 **Epidemiology, aetiology and pathophysiology***

Catheter-associated UTIs are the leading cause of secondary healthcare-associated bacteraemia. Approximately 20% of hospital-acquired bacteraemias arise from the urinary tract, and the mortality associated with this condition is approximately 10% [216]. A multistate point-prevalence survey of 11,282 patients across 183 hospitals reported that UTI accounted for 12.9% of healthcare acquired infections [217]. The incidence of bacteriuria associated with indwelling catheterisation is 3-8% per day [218-222]. The duration of catheterisation is the most important risk factor for the development of a CA-UTI [223, 224]. A systematic review and meta-analysis reported an average CA-UTI incidence of 13.79/1000 hospitalised patients with a prevalence of 9.33% [225]. This study also demonstrated that patients at high risk for CA-UTI were female, had a prolonged duration of catheterisation, had diabetes and had longer hospital and intensive care unit (ICU) stays [225].

Urinary catheterisation perturbs host defence mechanisms and provides easier access of uropathogens to the bladder. Indwelling urinary catheters facilitate colonisation with uropathogens by providing a surface for the attachment of host cell binding receptors recognised by bacterial adhesins, thus enhancing microbial adhesion. In addition, the uroepithelial mucosa is damaged, exposing new binding sites for bacterial adhesins, and residual urine in the bladder is increased through pooling below the catheter bulb [226]. Catheter-associated UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens.

*3.8.3 **Diagnostic evaluation***

3.8.3.1 Clinical diagnosis

Signs and systemic symptoms compatible with CA-UTI include new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute haematuria, pelvic discomfort and in those whose catheters have been removed dysuria, urgent or frequent urination and suprapubic pain or tenderness [205]. In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI [205, 206].

3.8.3.2 Laboratory diagnosis

Microbiologically, CA-UTI is defined by microbial growth of $\geq 10^3$ cfu/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours [206]. In catheterised patients, pyuria is not diagnostic for CA-UTI. The presence, absence, or degree of pyuria should not be used to differentiate CA-ABU from CA-UTI. Pyuria accompanying CA-ABU should not be interpreted as an indication for antimicrobial treatment. The absence of pyuria in a symptomatic patient suggests a diagnosis other than CA-UTI [206].

3.8.3.3 Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI

Summary of evidence	LE
Patients with indwelling or suprapubic catheters become carriers of ABU, with antibiotic treatment showing no benefit.	1a
In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI.	2
Microbiologically CA-UTI is defined by microbial growth of ≥ 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a mid-stream voided urine specimen from a patient whose catheter has been removed within the previous 48 hours.	3

Recommendations	Strength rating
Do not carry out routine urine culture in asymptomatic catheterised patients.	Strong
Do not use pyuria as sole indicator for catheter-associated UTI.	Strong
Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI.	Strong

3.8.4 ***Disease management***

3.8.4.1 Limiting catheterisation and appropriate catheter discontinuation

Indwelling catheters should be placed only when they are clinically indicated; for example, for management of urinary retention or where strict monitoring of fluid balance is required. Catheter restriction protocols are an important part of multi-modal interventions to reduce CA-UTI rates. Nurse-driven protocols in hospitals as well as community based multi-modal targeted infection programs have been proven to reduce CA-UTI rates [227, 228]. Adjunctive devices such as electronic reminder systems have also been shown to assist in prompt catheter removal in hospital settings (including non-ICU). A systematic review of nineteen different interventions to reduce UTI (including catheter discontinuation and limiting catheterisation), in nursing home patients reported successful CA-UTI reduction and reduced catheter usage [229]. Another report of over 2,800 patients on a surgical oncology unit found that increasing catheter bundle compliance resulted in a significant reduction in CA-UTI rates [230].

3.8.4.2 Urethral cleaning and chlorhexidine bathing

A network meta-analysis of 33 studies (6,490 patients) found no difference in the incidence of CA-UTI comparing the different urethral cleaning methods vs. disinfection [231]. The efficacy of chlorhexidine baths (either using 2% chlorhexidine-impregnated cloths or 4% chlorhexidine-based soap) in reducing CA-UTI is debatable. In a RCT of 10,783 ICU patients, no difference in CA-UTI rates were reported between chlorhexidine and control bathing groups [232]. However, a systematic review of fifteen studies involving only ICU patients reported that daily chlorhexidine bathing was associated with a significant reduction in CA-UTI (RR 0.68) [233].

3.8.4.3 Alternatives to indwelling urethral catheterisation

Alternatives include intermittent urethral catheterisation (IC) or suprapubic catheterisation. In a systematic review of patients undergoing gynaecological surgery, indwelling catheters were associated with higher rates of symptomatic UTIs compared to IC [234]. A further meta-analysis of postpartum women reported no difference in the incidence of UTI after labour between continuous catheterisation and IC [234]. A prospective cohort study of nursing home residents found that residents with a suprapubic catheter had fewer CA-UTIs and where hospitalised less, but were more likely to be colonised with multidrug-resistant organisms [235].

A Cochrane review found insufficient evidence to assess the value of different policies for replacing long-term urinary catheters on patient outcomes [88]. Another Cochrane review investigating the role of urethral (indwelling or intermittent) vs. suprapubic catheterisation in the short-term found inconclusive evidence of an effect on UTI rates [236]. For patients with neurogenic bladders, a further systematic review found no randomised or quasi-randomised controlled trials and therefore no conclusions regarding the use of the different types of catheter could be made [237]. Therefore, based on the available literature, while there are some limited studies showing a benefit of IC or suprapubic catheterisation over urethral catheterisation for CA-UTI rates, there is insufficient evidence to recommend those approaches routinely [238].

3.8.4.4 Impregnated or coated catheters

Hydrophilic coated catheters have been found to be beneficial for reducing CA-UTI rates. A meta-analysis of seven studies investigating RCTs comparing hydrophilic coated to PVC (standard) catheters for IC found a statistically lower risk ratio (0.84) for the frequency of UTI in the hydrophilic catheter group [239]. A systematic

review and practice policy statements on UTI prevention in patients with spina bifida recommended the use of single-use and hydrophilic catheters for IC [240].

Silver-alloy-impregnated catheters have not been associated with reduced CA-UTI rates. A small RCT of 54 ICU patients showed no significant difference in UTI rates between the silver-alloy impregnated group and the standard silicone foley catheter group [241]. In a cohort study of patients undergoing suprapubic catheter placement at the time of pelvic organ prolapsed surgery, a 5% difference in UTI rate at six weeks was noted, although this was not significant [242]. A systematic review of 26 trials (12,422 patients) reported that silver alloy-coated catheters were not associated with a statistically significant reduction in CA-UTI and were considerably more expensive [243]. However, the same study found that nitrofurazone-impregnated catheters reduce the risk of symptomatic CA-UTI; however, this was borderline significant (RR 0.84, 95% CI 0.71 to 0.99) [243]. A more recent RCT (214 patients) evaluating the use of nitrofurazone-infused catheters post-renal transplant found no benefit for their use [244]. Additionally, another RCT showed no benefit for the use of silver-alloy-coated indwelling catheters for reduction of UTI in 489 patients with spinal cord injury [245].

From a microbiological perspective, there may be a difference in organisms causing CA-UTI from urethral and suprapubic catheters and therefore urine culture results are important to guide therapy [238].

3.8.4.5 Antibiotic prophylaxis for catheter removal or insertion

The question of whether antibiotic prophylaxis reduces the rate of symptomatic UTI in adults following indwelling bladder catheter removal has been the subject of multiple RCTs. A review and meta-analysis identified seven RCTs with 1,520 participants. Meta-analysis showed overall benefit for use of prophylaxis RR (95%CI) = 0.45 (0.28-0.72); ARR 5.8% (from 10.5% to 4.7%) with a number needed to treat (NNT) of 17 [214]. Results for individual trials were inconsistent with five trials including the possibility of no benefit [214]. In an affectional RCT with 172 participants undergoing laparoscopic radical prostatectomy randomised to seven days of ciprofloxacin (n=80) or no treatment (n=80) at the time of catheter removal, which occurred at a mean of nine days post-operatively, there was no difference in infective complications recorded at up to four weeks after catheter removal. More isolates obtained from the prophylaxis group (11) were resistant to ciprofloxacin compared to the no treatment group (3) [215]. With regards to catheter insertion, a systematic review and meta-analysis showed that prophylactic antibiotics reduced the rate of bacteriuria and other signs of infection, such as pyuria, fever and gram-negative isolates in patients' urine, in surgical patients who undergo bladder drainage for at least 24 hours post-operatively [246].

3.8.4.6 Antibiotic prophylaxis for intermittent self-catheterisation (ISC)

An RCT investigating the effect of antibiotic prophylaxis in patients performing ISC showed that the frequency of symptomatic antibiotic-treated UTI was reduced by 48% using prophylaxis in a cohort of 404 patients performing ISC [247]. However, resistance against the antibiotics used for UTI treatment was more frequent in urinary isolates from the prophylaxis group than in those from the control group at nine to twelve months.

While the literature shows some benefit for reduction of CA-UTI by utilising antibiotics, the routine use of antibiotics for such a common procedure in the healthcare setting would result in an increased usage of antimicrobials. As highlighted in some of the RCTs this strategy is associated with increased antimicrobial resistance. Antibiotic use is the main driving force in the development of antimicrobial resistance. Current antimicrobial stewardship principles would not favour the routine use of antibiotic prophylaxis for either catheter changes or ISC even when UTIs could be prevented [238].

3.8.4.7 Antimicrobial treatment for suspected CA-UTI

A urine specimen for culture should be obtained prior to initiating antimicrobial therapy for presumed CA-UTI due to the wide spectrum of potential infecting organisms and the increased likelihood of antimicrobial resistance. The urine culture should be obtained from the freshly placed catheter prior to the initiation of antimicrobial therapy [206]. Based on the global prevalence on infections in urology (GPIU) study, the causative micro-organisms in CA-UTI are comparable with the causative micro-organisms in other cUTIs; therefore, symptomatic CA-UTIs should be treated according to the recommendations for cUTI (see section 3.7.5) [248].

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and fourteen days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterised or not [206]. A five-day regimen of levofloxacin may be considered in patients with CA-UTI who are not severely ill. Data are insufficient to make such a recommendation about other fluoroquinolones. With the rise in fluoroquinolone resistance, alternative antimicrobial agents should be selected where possible to start empirical therapy based on local microbiological information. A five-day antibiotic regimen with catheter exchange has been shown in one study to be non-inferior to a ten-day regimen with catheter retention on the basis of clinical cure [249].

A three-day antimicrobial regimen may be considered for women aged ≤ 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed. If an indwelling

catheter has been in place for two weeks at the onset of CA-UTI and is still indicated, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI. If use of the catheter can be discontinued, a culture of a voided mid-stream urine specimen should be obtained prior to the initiation of antimicrobial therapy to help guide treatment [206]. Long-term indwelling catheters should not be changed routinely. Follow appropriate practices for catheter insertion and care [250].

3.8.4.8 Recommendations for disease management and prevention of CA-UTI

Summary of evidence	LE
A systematic review of nineteen different interventions to reduce UTI including catheter discontinuation and limiting catheterisation in nursing home patients reported successful CA-UTI reduction and reduced catheter usage.	1b
A meta-analysis of seven studies investigating RCTs comparing hydrophilic coated to PVC (standard) catheters for IC found a statistically lower risk ratio (0.84) for the frequency of UTI in the hydrophilic catheter group.	1a
A meta-analysis showed overall benefit for use of prophylaxis for reduction of infective complications after catheter removal; however, results from individual trials were inconsistent with five out of seven trials including the possibility of no benefit.	1a
A subsequent RCT found no benefit of antibiotic prophylaxis for reduction of infective complications at up to four weeks after catheter removal.	1b

Recommendation	Strength rating
Treat symptomatic catheter-associated-UTI according to the recommendations for complicated UTI (see section 3.7.5).	Strong
Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed.	Strong
Do not treat catheter-associated asymptomatic bacteriuria in general.	Strong
Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions (e.g. transurethral resection of the prostate).	Strong
Replace or remove the indwelling catheter before starting antimicrobial therapy.	Strong
Do not apply topical antiseptics or antimicrobials to the catheter, urethra or meatus.	Strong
Do not use prophylactic antimicrobials to prevent catheter-associated UTIs.	Strong
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal.	Weak
The duration of catheterisation should be minimal.	Strong
Use hydrophilic coated catheters to reduce CA-UTI.	Strong
Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal or in patients performing intermittent self-catheterisation	Weak

3.9 Urosepsis

*3.9.1 **Introduction***

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a cUTI. Systemic inflammatory response syndrome (SIRS), characterised by fever or hypothermia, leukocytosis or leukopenia, tachycardia and tachypnoea, has been recognised as a set of alerting symptoms [251, 252]; however, SIRS is no longer included in the recent terminology of sepsis (Table 6) [12]. Mortality is considerably increased the more severe the sepsis is.

The treatment of urosepsis involves adequate life-supporting care, appropriate and prompt antimicrobial therapy, adjunctive measures and the optimal management of urinary tract disorders [253]. Source control by decompression of any obstruction and drainage of larger abscesses in the urinary tract is essential [253]. Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists.

Urosepsis is seen in both community-acquired and healthcare associated infections. Nosocomial urosepsis may be reduced by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urinary catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily aseptic techniques to avoid cross-infection.

Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation, presence of symptoms of organ dysfunction and persistent hypotension associated with tissue anoxia (Table 6).

*3.9.2 **Epidemiology, aetiology and pathophysiology***

Urinary tract infections can manifest from bacteriuria with limited clinical symptoms to sepsis or severe sepsis, depending on localised and potential systemic extension. It is important to note that a patient can move from an almost harmless state to severe sepsis in a very short time.

Mortality rates associated with sepsis vary depending on the organ source [254] with urinary tract sepsis generally having a lower mortality than that from other sources [255]. Sepsis is more common in men than in women [256]. In recent years, the overall incidence of sepsis arising from all sources has increased by 8.7% per year [254], but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000) [257]. Although the rate of sepsis due to Gram-positive and fungal organisms has increased, Gram-negative bacteria remain predominant in urosepsis [248, 258].

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include elderly patients, diabetics, immunosuppressed patients, such as transplant recipients and patients receiving cancer chemotherapy or corticosteroids. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can be affected by bacterial species that are capable of inducing inflammation within the urinary tract.

*3.9.3 **Diagnostic evaluation***

For diagnosis of systemic symptoms in sepsis either the full Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, or the quickSOFA score should be applied (Table 6). Microbiology sampling should be applied to urine, two sets of blood cultures [259], and if appropriate drainage fluids. Imaging investigations, such as sonography and CT-scan should be performed early [260].

Table 6. Definition and criteria of sepsis and septic shock [12, 251, 252]

Disorder	Definition
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical application, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. For rapid identification a quickSOFA (qSOFA) score was developed: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less.
Septic shock	Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

*3.9.4 **Physiology and biochemical markers***

E. coli remains the most prevalent micro-organism. In several countries, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [258]. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection.

3.9.4.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis [255]. They are molecules that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood [255].

3.9.4.2 Biochemical markers

Procalcitonin is the inactive pro-peptide of calcitonin. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels rise [261]. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin,

procalcitonin levels show only a moderate or no increase. Mid-regional proadrenomedulline is another sepsis marker. Mid-regional proadrenomedullin has been shown to play a decisive role in the induction of hyperdynamic circulation during the early stages of sepsis and progression to septic shock [262]. Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [261, 263]. In addition, serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [264]. Serum lactate should therefore also be monitored in patients with severe infections.

*3.9.5 **Disease management***

3.9.5.1 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Urosepsis treatment requires a combination of treatment including source control (obstruction of the urinary tract), adequate life-support care, and appropriate antimicrobial therapy [255, 260]. In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

3.9.5.1.1 Preventive measures of proven or probable efficacy

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections [265, 266] they include:

- Isolation of patients with multi-resistant organisms following local and national recommendations.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. Long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting [267]. Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

3.9.5.1.2 Appropriate peri-operative antimicrobial prophylaxis

For appropriate peri-operative antimicrobial prophylaxis see section 3.15. The potential side effects of antibiotics must be considered before their administration in a prophylactic regimen.

3.9.5.2 Treatment

Early goal-directed resuscitation was initially shown to improve survival for emergency department patients presenting with septic shock in a randomised, controlled, single-centre study [268]. However, follow-up studies in an improved emergency medicine background have not achieved positive effects with this strategy [269-271]. An individual patient data meta-analysis of the later three multicentre trials concluded that early goal-directed therapy did not result in better outcomes than usual care and was associated with higher hospitalisation costs [272].

3.9.5.2.1 Antimicrobial therapy

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available [253, 260]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with appropriate adjustment for renal function [253]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis [253].

3.9.5.2.2 Source control

Obstruction in the urinary tract is the most frequent urological source of urosepsis. Drainage of obstruction and abscesses, and removal of foreign bodies, such as urinary catheters or stones is therefore the most important source control strategy. These are key components of the strategy. This condition is an absolute emergency.

3.9.5.2.3 Adjunctive measures

The most important adjunctive measures in the management of sepsis are the following [253, 260]:

- fluid therapy with crystalloids, or albumin, if crystalloids are not adequately increasing blood pressure: passive leg raising-induced changes in cardiac output and in arterial pulse pressure are predictors of fluid responsiveness in adults [273];
- as vasopressors norepinephrine should be used primarily, dobutamine in myocardial dysfunction;
- hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of ≥ 65 mmHg;
- blood products should be given to target a haemoglobin level of 7-9 g/dL;
- mechanical ventilation should be applied with a tidal volume 6 mL/kg and plateau pressure ≤ 30 cm H_2O and a high positive end-expiratory pressure;
- sedation should be given minimally, neuromuscular blocking agents should be avoided;
- glucose levels should be target at ≤ 180 mg/dL;
- deep vein thrombosis prevention should be given with low-molecular weight heparin subcutaneously;
- stress ulcer prophylaxis should be applied in patients at risk, using protone pump inhibitors;
- enteral nutrition should be started early (< 48 hours).

In conclusion, sepsis in urology remains a severe situation with a considerable mortality rate. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next years [253, 260, 274]. Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antimicrobial treatment provide the best conditions for improving patient survival. The prevention of sepsis is dependent on good practice to avoid nosocomial infections and using antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

3.9.5.3 Summary of evidence and recommendations for the diagnosis and treatment of urosepsis

Summary of evidence	**LE**
Initial high dose empiric antimicrobial therapy, administered within the first hour, should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available.	2b
Source control interventions should be implemented as soon as possible to control or eliminate diagnosed and/or suspected infectious foci.	3

Recommendations	**Strength rating**
Perform the quickSOFA score to identify patients with potential sepsis.	Strong
Take a urine culture and two sets of blood cultures before starting antimicrobial treatment.	Strong
Administer parenteral high dose broad spectrum antimicrobials within the first hour after clinical assumption of sepsis.	Strong
Adapt initial empiric antimicrobial therapy on the basis of culture results.	Strong
Initiate source control including removal of foreign bodies, decompression of obstruction and drainage of abscesses in the urinary tract.	Strong
Provide immediate adequate life-support measures.	Strong

Table 7: Suggested regimens for antimicrobial therapy for urosepsis.

Antimicrobials	Daily dose	Duration of therapy
Cefotaxime	2 g t.i.d	7-10 days Longer courses are appropriate in patients who have a slow clinical response
Ceftazidime	1-2 g t.i.d	
Ceftriaxone	1-2 g q.d	
Cefepime	2 g b.i.d	
Piperacillin/tazobactam	4.5 g t.i.d	
Ceftolozane/tazobactam	1.5 g t.i.d	
Ceftazidime/avibactam	2.5 g t.i.d	
Gentamicin*	5 mg/kg q.d	
Amikacin*	15 mg/kg q.d	
Ertapenem	1 g q.d	
Imipenem/cilastatin	0.5 g t.i.d	
Meropenem	1 g t.i.d	

** Not studied as monotherapy in urosepsis*
b.i.d = twice daily; t.i.d = three times daily; q.d = every day.

3.10 Urethritis

*3.10.1 **Introduction***

Urethritis can be of either infectious or non-infectious origin. Inflammation of the urethra presents usually with LUTS and must be distinguished from other infections of the lower urinary tract. Urethral infection is typically spread by sexual contact.

*3.10.2 **Epidemiology, aetiology and pathogenesis***

From a therapeutic and clinical point of view, gonorrhoeal urethritis (GU) caused by *Neisseria gonorrhoeae* must be differentiated from non-gonococcal urethritis (NGU). Non-gonococcal urethritis is a non-specific diagnosis that can have many infectious aetiologies. Causative pathogens include *Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum* and *Trichomonas vaginalis*. The role of Ureaplasma spp. as urethritis causative pathogens is controversial. Recent data suggests that *U. urealyticum*, but not *U. parvum* is an aetiological agent in NGU [275]. The prevalence of isolated causative pathogens are: *C. trachomatis* 11-50%; *M. genitalium* 6-50%; Ureaplasmas 5-26%; *T. vaginalis* 1-20%; and adenoviruses 2-4% [276].

Causative agents either remain extracellularly on the epithelial layer or penetrate into the epithelium (*N. gonorrhoeae* and *C. trachomatis*) and cause pyogenic infection. Although arising from urethritis, chlamydiae and gonococci can spread further through the urogenital tract to cause epididymitis in men or cervicitis, endometritis and salpingitis in women [277].

Mucopurulent or purulent discharge, dysuria and urethral pruritus are symptoms of urethritis. However, many infections of the urethra are asymptomatic.

*3.10.3 **Evidence Summary***

A systematic search of the literature form January 2014 until February 2019 identified 488 titles of which 71 were selected for full text review. Thirteen systematic reviews or guidelines based on systematic literature searches [275-287], and seventeen original publications [288-304] were selected for further analysis. In addition, a further eleven relevant publications were identified from the references of the reviewed literature [305-315]. The evidence questions addressed were:

1. In patients with urethritis what is the best method of detecting the causative pathogen?
2. In patients with urethritis what are the best treatment strategies for clinical or microbiological cure?

*3.10.4 **Diagnostic evaluation***

In symptomatic patients the diagnosis of urethritis can be made based on the presence of any of the following criteria [276, 277]:

- Mucoid, mucopurulent, or purulent urethral discharge.
- Gram or methylene-blue stain of urethral secretions demonstrating inflammation. Five or more polymorphonuclear leucocytes (PMNL) per high power field (HPF) is the historical cut-off for the diagnosis of urethritis. A threshold of ≥ 2 PMNL/HPF was proposed recently based on better diagnostic accuracy [292, 305-307], but this was not supported by other studies [291]. Therefore, in line with the 2016 European Guideline on the management of NGU [276] the use of ≥ 5 PMNL/HPF cut-off level is recommended until the benefit of alternative cut-off levels is confirmed.

- The presence of ≥ 10 PMNL/HPF in the sediment from a spun first-void urine sample or a positive leukocyte esterase test in first-void urine.

Evidence of urethral inflammation in the Gram stain of urethral secretions with gonococci located intracellularly as Gram-negative diplococci indicates GU. Non-gonococcal urethritis is confirmed when staining of urethral secretions indicates inflammation in the absence of intracellular diplococci. Clinicians should always perform point-of-care diagnostics (e.g. Gram staining, first-void urine with microscopy, leukocyte esterase testing) if available to obtain objective evidence of urethral inflammation and to guide treatment [276, 277, 290]. Recent studies showed that processing time of point-of-care diagnostics is highly relevant in terms of patient compliance and real-life applicability [288, 289].

Men who meet the criteria for urethritis should be tested for *C. trachomatis*, *M. genitalium* and *N. gonorrhoea* with nucleic acid amplification tests (NAAT), even if point-of-care tests are negative for gonorrhoeae [276, 279]. The sensitivity and specificity of NAATs is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections [280, 308]. The performance of first-catch urine is non-inferior to urethral swabs [308]. In case of delayed treatment, if a NAAT is positive for gonorrhoea, a culture using urethral swabs should be performed before treatment to assess the antimicrobial resistance profile of the infective strain [277]. *N. gonorrhoeae* and *C. trachomatis* cultures are mainly used to evaluate treatment failures and monitor developing resistance to current treatment. Trichomonas spp. can usually be identified microscopically [277] or by NAATs [282].

Non-gonococcal urethritis is classified as persistent when symptoms do not resolve within three to four weeks following treatment. When this occurs NAATs should be performed for urethritis pathogens including *T. vaginalis* four weeks after completion of therapy [276, 293].

3.10.5 ***Disease management***

For severe urethritis empirical treatment should be started following diagnosis. If the patients symptoms are mild, delayed treatment guided by the results of NAATs is recommended. All sexual partners at risk should be assessed and treated whilst maintaining patient confidentiality [276, 296].

3.10.5.1 Gonococcal urethritis

For GU, a combination treatment using two antimicrobials with different mechanisms of action is recommended to improve treatment efficacy and to hinder increasing resistance to cephalosporins [277]. Ceftriaxone 1 g intramuscularly or intravenously with azithromycin 1 g single oral dose should be used as first-line treatment. Azithromycin is recommended because of its favourable susceptibility rates compared to other antimicrobials, good compliance with the single-dose regimen and the possibility of a *C. trachomatis* co-infection [277]. In case of azithromycin allergy, doxycycline can be used instead in combination with ceftriaxone or cefixime [277]. A 400 mg oral dose of cefixime is recommended as an alternative regimen to ceftriaxone; however, it has less favourable pharmacodynamics and may lead to the emergence of resistance [278, 314].

A number of alternative regimens for the treatment of GU have been studied. In a randomised, open label, non-comparative clinical study dual treatment with a combination of intramuscular gentamicin 240 mg plus oral azithromycin 2 g (n=202) single doses and a combination of oral gemifloxacin 320 mg plus oral azithromycin 2 g (n=199) single doses were associated with microbiological cure rates of 100% and 99.5%, respectively [310]. A 2014 systematic review focusing on the use of single-dose intramuscular gentamicin concluded that there is insufficient data to support or refute the efficacy and safety of this regimen in the treatment of uncomplicated gonorrhoea [284]. In three prospective single arm studies enrolling men with GU the use of extended-release azithromycin 2 g single oral dose resulted in microbiological cure rates of 83% (n=36), 93.8% (n=122) and 90.9% (n=33), respectively [300, 301, 303]. However, azithromycin monotherapy is generally not recommended because of its effect on increasing macrolide resistance rates [277]. Intramuscular spectinomycin 2 g single dose shows microbiological cure rates above 96% [311, 314] in urogenital gonorrhoeal infections; therefore, where available, it can be a valid treatment alternative. An open label, randomised trial compared oral fosfomycin trometamol 3 g on days one, three and five (n=60) with intramuscular ceftriaxone 250 mg plus oral azithromycin 1 g single dose (n=61) in men with uncomplicated GU. In the per-protocol analysis clinical and microbiologic cure rates were 96.8% and 95.3% respectively [304].

The worldwide increase in gonorrhoeal antimicrobial resistance and the emergence of multidrug-resistant gonorrhoeal strains is a globally recognised healthcare crisis which emphasises the importance of guideline adherence [283, 295, 315].

3.10.5.2 Non-gonococcal urethritis

For NGU without an identified pathogen oral doxycycline 100 mg twice daily for seven days should be used as first-line treatment. Alternatively, single dose oral azithromycin 500 mg day one and 250 mg days two

to four can be used. This regimen provides better efficacy compared to azithromycin 1 g single dose for *M. genitalium* infections, in which azithromycin 1 g single dose treatment is associated with the development of increasing macrolide resistance significantly decreasing the overall cure rate [276, 279, 285, 299]. However, a retrospective cohort study did not find significant difference between the extended and 1 g single dose azithromycin regimen regarding cure rates and the selection of macrolide resistance in *M. genitalium* urethritis [297]. If macrolide resistant *M. genitalium* is detected moxifloxacin 400 mg can be used for seven to fourteen days [276, 277, 286]. In case of failure after both azithromycin and moxifloxacin treatment, pristinamycin (registered in France) is the only antimicrobial agent with documented activity against *M. genitalium* [279, 298, 309]. Josamycin 500 mg three times a day for ten days is used in Russia, but will not eradicate macrolide-resistant strains [279].

For chlamydial urethritis azithromycin 1 g single dose and doxycycline 100 mg twice daily for seven days are both effective options [313]. A Cochrane review found that in men with urogenital *C. trachomatis* infection regimens with azithromycin are probably less effective than doxycycline for microbiological failure, however, there might be little or no difference for clinical failure [287]. Fluoroquinolones, such as ofloxacin or levofloxacin, may be used as second-line treatment only in selected cases where the use of other agents is not possible [312].

For *U. urealyticum* infections the efficacy of doxycycline 100 mg twice daily for seven days is similar to azithromycin 1 g single dose treatment [276, 294]. For urethritis caused by *T. vaginalis* oral metronidazole or tinidazole 2 g single dose is recommended as first-line treatment. For treatment options for persistent or recurrent *T. vaginalis* infection refer to the review of Sena *et al.,* [282].

In case of persistent NGU treatment should cover *M. genitalium* and *T. vaginalis* [276, 277].

3.10.6 ***Follow-up***

Patients should be followed up for control of pathogen eradication after completion of therapy only if therapeutic adherence is in question, symptoms persist or reoccurrence is suspected. Patients should be instructed to abstain from sexual intercourse for seven days after therapy is initiated, provided their symptoms have resolved and their sexual partners have been adequately treated. Reporting and source tracing should be done in accordance with national guidelines and in cooperation with specialists in venereology, whenever required. Persons who have been diagnosed with a new STD should receive testing for other STDs, including syphilis and HIV [281].

3.10.7 ***Summary of evidence and recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis***

Summary of evidence	**LE**
A Gram stain of urethral discharge or a urethral smear that shows ≥ 5 PMNL/HPF and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis.	3b
Validated NAATs of first-void urine samples have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections.	2a
For GU dual treatment with ceftriaxone and azithromycin is the most effective combination.	2a
In case of urogenital *C. trachomatis* infection in men azithromycin is probably less effective than doxycycline for microbiological failure; however, there might be little or no difference for clinical failure.	1a
In case of *U. urealyticum* infection the efficacy of doxycycline 100 mg twice for seven days is similar to azithromycin 1 g single dose treatment.	2a

Recommendations	**Strength rating**
Perform a Gram stain of urethral discharge or a urethral smear to preliminarily diagnose gonococcal urethritis.	Strong
Perform a validated nucleic acid amplification test (NAAT) on a first-void urine sample or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections.	Strong
Delay treatment until the results of the NAATs are available to guide treatment choice in patients with mild symptoms.	Strong
Perform a urethral swab culture, prior to initiation of treatment, in patients with a positive NAAT for gonorrhoea to assess the antimicrobial resistance profile of the infective strain.	Strong
Use a pathogen directed treatment based on local resistance data.	Strong
Sexual partners should be treated maintaining patient confidentiality.	Strong

Table 8: Suggested regimens for antimicrobial therapy for urethritis

Pathogen	Antimicrobial	Dosage & Duration of therapy	Alternative regimens
Gonococcal Infection	Ceftriaxone Azithromycin	1 g i.m. or i.v.*, SD 1 g p.o., SD	• Cefixime 400 mg p.o., SD plus Azithromycin 1 g p.o., SD In case of cephalosporin allergy: • Gentamicin 240 mg i.m SD plus Azithromycin 2 g p.o., SD • Gemifloxacin 320 mg p.o., SD plus Azithromycin 2 g p.o., SD • Spectinomycin 2 g i.m., SD • Fosfomycin trometamol 3 g p.o. on days 1, 3 and 5 In case of azithromycin allergy, in combination with ceftriaxone or cefixime: • Doxycycline 100 mg b.i.d, p.o., 7 days
Non-Gonococcal infection (non-identified pathogen)	Doxycycline	100 mg b.i.d, p.o., 7 days	Azithromycin 500 mg p.o., day 1, 250 mg p.o., 4 days
Chlamydia trachomatis	Azithromycin Or Doxycycline	1.0-1.5 g p.o., SD 100 mg b.i.d, p.o., for 7 days	• Levofloxacin 500 mg p.o., q.d., 7 days • Ofloxacin 200 mg p.o., b.i.d., 7 days
Mycoplasma genitalium	Azithromycin	500 mg p.o., day 1, 250 mg p.o., 4 days	In case of macrolide resistance: • Moxifloxacin 400 mg q.d., 7-14 days
Ureaplasma urealyticum	Doxycycline	100 mg b.i.d, p.o., 7 days	Azithromycin 1.0-1.5 g p.o., SD
Trichomonas vaginalis	Metronidazole Tinidazole	2 g p.o., SD 2 g p.o., SD	Metronidazole 500 mg p.o., b.i.d., 7 days
Persistent non-gonococcal urethritis			
After first-line doxycycline	Azithromycin plus Metronidazole	500 mg p.o., day 1, 250 mg p.o., 4 days 400 mg b.i.d. p.o., 5 days	If macrolide resistant *M. genitalium* is detected moxifloxacin should be substituted for azithromycin
After first-line azithromycin	Moxifloxacin plus Metronidazole	400 mg p.o. q.d., 7-14 days 400 mg b.i.d. p.o., 5 days	

SD = single dose; b.i.d = twice daily; q.d = everyday; p.o. = orally; i.m. = intramuscular; i.v. = intravenous.
** Despite the lack of RCTs there is increasing evidence that intravenous treatment with ceftriaxone is safe and effective for the treatment of gonorrhoeal infections and avoids the discomfort of an intramuscular injection for patients [316].*

3.11 Bacterial Prostatitis

*3.11.1 **Introduction***

Bacterial prostatitis is a clinical condition caused by bacterial pathogens. It is recommended that urologists use the classification suggested by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), in which bacterial prostatitis, with confirmed or suspected infection, is distinguished from chronic pelvic pain syndrome (CPPS) (Table 9) [317-319].

Table 9: Classification of prostatitis and CPPS according to NIDDK/NIH [317-319]

Type	Name and description
I	Acute bacterial prostatitis (ABP)
II	Chronic bacterial prostatitis (CBP)
III	Chronic non-bacterial prostatitis – CPPS
IIIA	Inflammatory CPPS (white cells in semen/EPS/VB3)
IIIB	Non-inflammatory CPPS (no white cells in semen/EPS/VB3)
IV	Asymptomatic inflammatory prostatitis (histological prostatitis)

CPPS = chronic pelvic pain syndrome; EPS = expressed prostatic secretion; VB3 = voided bladder urine specimen 3 (urine following prostatic massage).

*3.11.2 **Evidence Summary***

A systematic literature search from 1980 until June 2017 was performed. One systematic review [320], six RCTs [321-326], two narrative reviews [327, 328], one prospective cohort study [329], two prospective cross-sectional studies [330, 331], and one retrospective cohort study [323], were selected from 856 references.

A retrospective study [332], investigated the potential role of unusual pathogens in prostatitis syndrome in 1,442 patients over a four year period. An infectious aetiology was determined in 74.2% of patients; *C. trachomatis, T. vaginalis* and *U. urealyticum* infections were found in 37.2%, 10.5% and 5% of patients, respectively whilst *E. coli* infection was found in only 6.6% of cases. Cross sectional studies confirmed the validity of the Meares and Stamey test to determine the bacterial strain and targeted antibiotic therapies [330, 331]. The evidence levels were good, in particular those regarding information on atypical strains, epidemiology and antibiotic treatments.

A systematic review on antimicrobial therapy for CBP [320] compared multiple antibiotic regimens from eighteen selected studies enrolling a total of 2,196 patients. The role of fluoroquinolones as first-line agents was confirmed with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events. The efficacy of macrolides and tetracyclines on atypical pathogens was confirmed.

Randomised controlled trials on combined treatments [325, 326] indicated that the combination of plants/herbal extracts or PDE5Is with antibiotics may improve quality of life and symptoms in patients with CBP; however, the number of enrolled patients was inadequate to obtain definitive conclusions.

A review of treatment of bacterial prostatitis [327] indicated that the treatment of CBP is hampered by the lack of an active antibiotic transport mechanism into infected prostate tissue and fluids. The review underlined the potential effect of different compounds in the treatment of ABP and CBP on the basis of over 40 studies on the topic.

One RCT compared the effects of two different metronidazole regimens for the treatment of CBP caused by *T. vaginalis* [324]. Metronidazole 500 mg three times daily for fourteen days was found to be efficient for micro-organism eradication in 93.3% of patients with clinical failure in 3.33% of cases. The evidence question addressed was: In men with NIDDK/NIH Category I or II prostatitis what is the best antimicrobial treatment strategy for clinical resolution and eradication of the causative pathogen?

*3.11.3 **Epidemiology, aetiology and pathogenesis***

Prostatitis is a common diagnosis, but less than 10% of cases have proven bacterial infection [228]. *Enterobacterales*, especially *E. coli*, are the predominant pathogens in ABP [333]. In CBP, the spectrum of species are wider and may include atypical micro-organisms [327]. In patients with immune deficiency or HIV infection, prostatitis may be caused by fastidious pathogens, such as *M. tuberculosis, Candida spp*. and other rare pathogens, such as *Coccidioides immitis, Blastomyces dermatitidis*, and *Histoplasma capsulatum* [334]. The significance of identified intracellular bacteria, such as *C. trachomatis*, is uncertain [335]; however, two studies have highlighted its possible role as a causative pathogen in CBP [336, 337].

*3.11.4 **Diagnostic evaluation***

3.11.4.1 History and symptoms

Acute bacterial prostatitis usually presents abruptly with voiding symptoms and distressing but poorly localised pain. It is often associated with malaise and fever. Transrectal prostate biopsy increases the risk of ABP despite antibiotic prophylaxis and antiseptic prevention procedures [321]. Chronic bacterial prostatitis is defined by symptoms that persist for at least three months [338-340]. The predominant symptoms are pain at various locations including the perineum, scrotum, penis and inner part of the leg as well as LUTS [317-319].

3.11.4.2 Symptom questionnaires

In CBP symptoms appear to have a strong basis for use as a classification parameter [341]. Prostatitis symptom questionnaires have therefore been developed to assess severity and response to therapy [341, 342]. They include the validated Chronic Prostatitis Symptom Index (CPSI); however, its usefulness in clinical practice is uncertain [329].

3.11.4.3 Clinical findings

In ABP, the prostate may be swollen and tender on DRE. Prostatic massage should be avoided as it can induce bacteraemia and sepsis. Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% [343]. Blood culture and complete blood count are useful in ABP. Imaging studies can detect a suspected prostatic abscess [327].

In case of longer lasting symptoms CPPS as well as other urogenital and anorectal disorders must be taken into consideration. Symptoms of CBP or CPPS can mask prostate tuberculosis. Pyospermia and hematospermia in men in endemic regions or with a history of tuberculosis should trigger investigation for urogenital tuberculosis.

3.11.4.4 Urine cultures and expressed prostatic secretion

The most important investigation in the evaluation of a patient with ABP is mid-stream urine culture [327]. In CBP, quantitative bacteriological localisation cultures and microscopy of the segmented urine and expressed prostatic secretion (EPS), as described by Meares and Stamey [344], are still important investigations to categorise clinical prostatitis [330, 331]. Accurate microbiological analysis of samples from the Meares and Stamey test may also provide useful information on the presence of atypical pathogens such as *C. trachomatis, T. vaginalis* and *U. urealiticum* [332]. The two-glass test has been shown to offer similar diagnostic sensitivity to the four-glass test [345].

3.11.4.5 Prostate biopsy

Prostate biopsies cannot be recommended as routine work-up and are not advisable in patients with untreated bacterial prostatitis due to the increased risk of sepsis.

3.11.4.6 Other tests

Transrectal US may reveal endoprostatic abscesses, calcification in the prostate, and dilatation of the seminal vesicles; however, it is unreliable as a diagnostic tool for prostatitis [346].

3.11.4.7 Additional investigations

3.11.4.7.1 Ejaculate analysis

Performing an ejaculated semen culture improves the diagnostic utility of the four-glass test [330]; however, semen cultures are more often positive than EPS cultures in men with non-bacterial prostatitis [331]. Bladder outflow and urethral obstruction should always be considered and ruled out by uroflowmetry, retrograde urethrography, or endoscopy.

3.11.4.7.2 First-void urine sample

First-void urine is the preferred specimen for the diagnosis of urogenital *C. trachomatis* infection in men by NAATs, since it is non-invasive and yet allows the detection of infected epithelial cells and associated *C. trachomatis* particles [347].

3.11.4.7.3 Prostate specific antigen (PSA)

Prostate specific antigen is increased in about 60% and 20% of men with ABP and CBP, respectively [328]. The PSA level decreases after antibiotic therapy (which occurs in approximately 40% of patients) and correlates with clinical and microbiological improvement [322]. Measurement of free and total PSA adds no practical diagnostic information in prostatitis [348].

3.11.4.8 Summary of evidence and recommendations for the diagnosis of bacterial prostatitis

Summary of evidence	**LE**
Urine dipstick testing for nitrite and leukocytes has a positive predictive value of 95% and a negative predictive value of 70% in patients with ABP.	3
The four-glass Meares and Stamey test is the optimum test for diagnosis of CBP. The two-glass test has been shown to offer similar diagnostic sensitivity in a comparison study.	2b
First-void urine is the preferred specimen for the diagnosis of urogenital *C. trachomatis* infection in men by NAATs.	2b

Transrectal ultrasound is unreliable and cannot be used as a diagnostic tool in prostatitis.	3
Semen culture sensitivity is reported to be approximately 50%; therefore, it is not routinely part of the diagnostic assessment of CBP.	3
Prostate specific antigen levels may be elevated during active prostatitis; therefore, PSA testing should be avoided as it offers no practical diagnostic information for prostatitis.	3

Recommendations	Strength rating
Do not perform prostatic massage in acute bacterial prostatitis (ABP).	Strong
Take a mid-stream urine dipstick to check nitrite and leukocytes in patients with clinical suspicion of ABP.	Weak
Take a mid-stream urine culture in patients with ABP symptoms to guide diagnosis and tailor antibiotic treatment.	Weak
Take a blood culture and a total blood count in patients presenting with ABP.	Weak
Perform accurate microbiological evaluation for atypical pathogens such as *Chlamydia trachomatis* or Mycoplasmata in patients with chronic bacterial prostatitis (CBP).	Weak
Perform the Meares and Stamey 2- or 4-glass test in patients with CBP.	Strong
Perform transrectal ultrasound in selected cases to rule out the presence of prostatic abscess.	Weak
Do not routinely perform microbiological analysis of the ejaculate alone to diagnose CBP.	Weak

*3.11.5 **Disease management***

3.11.5.1 Antimicrobials

Antimicrobials are life-saving in ABP and recommended in CBP. Culture-guided antibiotic treatments are the optimum standard; however, empirical therapies should be considered in all patients with ABP.

In ABP parenteral administration of high doses of bactericidal antimicrobials, such as broad-spectrum penicillins, a third-generation cephalosporin or fluoroquinolones, is recommended [349]. For initial therapy, any of these antimicrobials may be combined with an aminoglycoside [333-342, 349-353]. Ancillary measures include adequate fluid intake and urine drainage [228]. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks [354].

Fluoroquinolones, despite the high resistance rates of uropathogens, are recommended as first-line agents in the empirical treatment of CBP because of their favourable pharmacokinetic properties [355], their generally good safety profile and antibacterial activity against Gram-negative pathogens including *P. aeruginosa* and *C. trachomatis* [320, 356]. However, increasing bacterial resistance is a concern. Azithromycin and doxycycline are active against atypical pathogens such as *C. trachomatis* and genital mycoplasmata [323, 332]. Levofloxacin did not demonstrate significant clearance of *C. trachomatis* in patients with CBP [357]. Metronidazole treatment is indicated in patients with *T. vaginalis* infections [324].

Duration of fluoroquinolone treatment must be at least fourteen days while azithromycin and doxycycline treatments should be extended to at least three to four weeks [323, 332]. In CBP antimicrobials should be given for four to six weeks after initial diagnosis [327]. If intracellular bacteria have been detected macrolides or tetracyclines should be given [320, 355, 358].

3.11.5.2 Intraprostatic injection of antimicrobials

This treatment has not been evaluated in controlled trials and should not be considered [359, 360].

3.11.5.3 Combined treatments

A combination of fluoroquinolones with various herbal extracts may attenuate clinical symptoms without increasing the rate of adverse events [325]. However, a combination of fluoroquinolones with vardenafil did not improved microbiological eradication rates or attenuated pain or voiding symptoms in comparison with fluoroquinolone treatment alone [326].

3.11.5.4 Drainage and surgery

Approximately 10% of men with ABP will experience urinary retention [361] which can be managed by uretheral or suprapubic catheterisation. However, recent evidence suggests that suprapubic catheterisation can reduce the risk of development of CBP [362].

In case of prostatic abscess, both drainage and conservative treatment strategies appear feasible [363]; however, the abscess size may matter. In one study, conservative treatment was successful if the abscess cavities were < 1 cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage [364].

3.11.5.5 Summary of evidence and recommendations for the disease management of bacterial prostatitis

Summary of evidence	LE
The treatment regimen for ABP is based on clinical experience and a number of uncontrolled clinical studies. For systemically ill patients with ABP, parenteral antibiotic therapy is preferable. After normalisation of infection parameters, oral therapy can be substituted and continued for a total of two to four weeks.	3
The role of fluoroquinolones as first-line agents for antimicrobial therapy for CBP was confirmed in a systematic review, with no significant differences between levofloxacin, ciprofloxacin and prulifloxacin in terms of microbiological eradication, clinical efficacy and adverse events.	1a
Metronidazole 500 mg three times daily for fourteen days was found to be efficient for eradication in 93.3% of patients with *T. vaginalis* CBP.	1b
In patients with CBP caused by obligate intracellular pathogens, macrolides showed higher microbiological and clinical cure rates compared to fluoroquinolones.	1a
Clinicians should consider local drug-resistance patterns when choosing antibiotics.	3

Recommendations	Strength rating
Acute bacterial prostatitis	
Treat acute bacterial prostatitis according to the recommendations for complicated UTIs (see section 3.7.5).	Strong
Chronic bacterial prostatitis (CBP)	
Prescribe a fluoroquinolone (e.g. ciprofloxacin, levofloxacin) as first-line treatment for CBP.	Strong
Prescribe a macrolide (e.g. azithromycin) or a tetracycline (e.g. doxycycline) if intracellular bacteria have been identified as the causative agent of CBP.	Strong
Prescribe metronidazole in patients with *Trichomonas vaginalis* CBP.	Strong

Table 10: Suggested regimens for antimicrobial therapy for chronic bacterial prostatitis

Antimicrobial	Daily dose	Duration of therapy	Comments
Floroquinolone	Optimal oral daily dose	4-6 weeks	
Doxycycline	100 mg b.i.d	10 days	Only for *C. trachomatis* or mycoplasma infections
Azithromycin	500 mg once daily	3 weeks	Only for *C. trachomatis* infections
Metronidazole	500 mg t.i.d.	14 days	Only for *T. vaginalis* infections

b.i.d = twice daily; t.i.d = three times daily.

3.11.6 ***Follow-up***

In asymptomatic post-treatment patients routine urinalysis and/or urine culture is not mandatory as there are no validated tests of cure for bacterial prostatitis except for cessation of symptoms [327]. In patients with persistent symptoms and repeated positive microbiological results for sexually transmitted infectious pathogens, microbiological screening of the patient's partner/s is recommended. Antibiotic treatments may be repeated with a more prolonged course, higher dosage and/or different compounds [327].

3.12 Acute Infective Epididymitis

3.12.1 ***Epidemiology, Aetiology and Pathophysiology***

Epididymitis is a common condition with incidence ranging from 25 to 65 cases per 10,000 adult males per year and can be acute, chronic or recurrent [365]. Acute epididymitis is clinically characterised by pain, swelling and increased temperature of the epididymis, which may involve the testis and scrotal skin. It is generally caused by migration of pathogens from the urethra or bladder that can be identified by appropriate diagnostics in up to 90% of patients [366]. Torsion of the spermatic cord (testicular torsion) is the most important differential diagnosis in boys and young men.

The predominant pathogens isolated are *Enterobacterales* (typically *E. coli*), *C. trachomatis* and *N. gonorrhoeae* [367]. Men who have anal intercourse and those with abnormalities of the urinary tract resulting in bacteriuria are at higher risk of epididymitis caused by *Enterobacterales* [368]. The mumps virus should be

considered if there are viral prodromal symptoms and salivary gland enlargement. Tuberculous epididymitis may occur, typically as chronic epididymitis, in high-risk groups such as men with immunodeficiency and those from high prevalence countries, it frequently results in a discharging scrotal sinus. *Brucella* or *Candida spp*. are rare possible pathogens.

3.12.2 ***Diagnostic Evaluation***

Culture of a mid-stream specimen of urine should be performed and any previous urine culture results should be checked. Sexually transmitted infections including *C. trachomatis* or *N. gonorrhoeae* should be detected by NAAT on first-voided urine or urethral swab. A urethral swab or smear should be performed for Gram staining and culture of *N. gonorrhoeae*, when available [365, 369, 370]. Detection of these pathogens should be reported according to local procedures. All patients with probable sexually transmitted infections (STIs) should be advised to attend an appropriate clinic to be screened for other STIs. Men with *Enterobacterales* may require investigation for lower urinary tract abnormalities. If tuberculous epididymitis is suspected, three sequential early morning urine samples should be cultured for acid-fast bacilli (AFB) and sent for screening by NAAT for *M. tuberculosis* DNA [371]. If appropriate, prostate secretion, ejaculate, discharge from a draining scrotal fistula, as well as fine needle aspiration and biopsy specimens should be investigated using microscopy, AFB culture and NAAT. Scrotal US is more accurate for the diagnose of acute epididymitis than urinalysis alone [372] and may also be beneficial for the exclusion of other pathologies [373].

3.12.3 ***Disease Management***

Men with suspected STI should be informed of the risks to others and advised not to have sex until free of infection. Empirical antimicrobial therapy has to be chosen with consideration of the most probable pathogen and degree of penetration into the inflamed epididymis and may need to be varied according to local pathogen sensitivities and guidance. Generally, both *C. trachomatis* and *Enterobacterales* should be covered initially and the regimen modified according to pathogen identification. Doxycycline and some specific fluoroquinolones have good clinical and microbiological cure rates in patients with suspected *C. trachomatis* or *M. genitalium* and both achieve adequate levels in inflamed male genital tissues with oral dosing. Macrolide antibiotics such as azithromycin are effective against *C. trachomatis* but have not been tested in epididymitis; however, initial pharmacokinetic studies suggest that azithromycin may effectively penetrate epididymal tissue when given in multiple doses [374]. Fluoroquinolones remain effective for oral treatment of *Enterobacterales* although resistance is increasing and local advice should be sought. Fluoroquinolones should not be considered for gonorrhoea. Single high parenteral dose of a third generation cephalosporin is effective against *N. gonorrhoeae*; current resistance patterns and local public health recommendations should guide choice of agent.

Clinical response to antibiotics in men with severe epididymitis should be assessed after approximately three days. Men with likely or proven STI should be assessed at fourteen days to check cure and ensure tracing and treatment of contacts according to local public health recommendations.

3.12.4 ***Evidence Summary***

Relating to this chapter, four guidelines based on systematic reviews were identified [277, 369, 375, 376]. No evidence quality assessments were detailed. A high quality RCT demonstrated that a ten-day course of ciprofloxacin was superior to pivampicillin for clinical cure (80% vs. 60%) in men aged > 40 years [377]. Data from a large comparative case series suggested that young age and history of sexual activity are not sufficiently predictive of a sexually transmitted pathogen to guide antibiotic treatment in acute epididymitis [366].

Empiric antibiotic regimens from existing guidelines [277, 369, 375, 376] and panel consensus:

1. For men with acute epididymitis at low risk of gonorrhoea (e.g. no discharge) a single agent or combination of two agents of sufficient dose and duration to eradicate *C. trachomatis* and *Enterobacterales* should be used. Appropriate options are:

    A. A fluoroquinolone active against *C. trachomatis* orally once daily for ten to fourteen days*

    OR

    B. Doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days* **plus** an antibiotic active against *Enterobacterales*** for ten to fourteen days*

2. For men with likely gonorrhoeal acute epididymitis a combination regimen active against Gonococcus and *C. trachomatis* must be used such as:

    A. Ceftriaxone 1000 mg intramuscularly single dose **plus** doxycycline 200 mg initial dose by mouth and then 100 mg twice daily for ten to fourteen days*

3. For non-sexually active men with acute epididymitis a single agent of sufficient dose and duration to eradicate *Enterobacterales* should be used. Appropriate option is a fluoroquinolone by mouth once daily for ten to fourteen days*

**Depending upon pathogen identification and clinical response.*
*** A parenteral option will be required for men with severe infection requiring hospitalisation.*

Surgical exploration may be required to drain abscesses or debride tissue. A comparative cohort study found that lack of separation of epididymis and testis on palpation and the presence of abscess on US may predict requirement for surgery following initial antibiotic treatment [378].

A cohort study found semen parameters may be impaired during epididymitis but recovered following successful treatment [379]. Comparative clinician cohort studies suggest adherence to guidelines for assessment and treatment of epididymitis is low, particularly by urologists compared to sexual health specialists [380] and by primary care physicians [381].

*3.12.5 **Screening***

A large cohort screening study for carriage of *C. trachomatis* including a randomly selected group of 5,000 men of whom 1,033 were tested showed no benefit in terms of reduction in risk of epididymitis over nine years of observation [382].

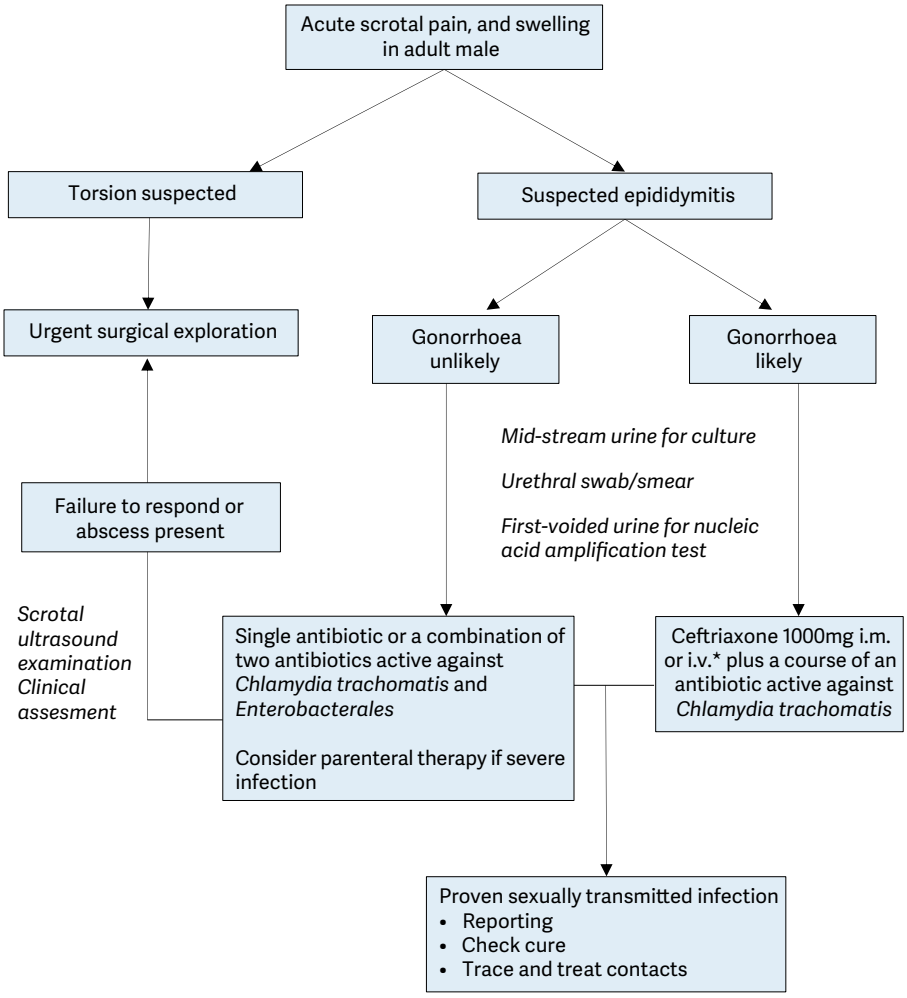
*3.12.6 **Summary of evidence and recommendations for the diagnosis and treatment of acute infective epididymitis***

Summary of evidence	**LE**
In young sexually active patients both STIs and *Enterobacterales* have to be considered as aetiological agents.	3
In patients > 40 years antibiotic therapy with ciprofloxacin is superior to pivmecillinam.	1b
A negative sexual risk history does not exclude STIs in sexually active men.	3

Recommendations	**Strength rating**
Obtain a mid-stream urine and a first-voided urine sample for pathogen identification by culture and nucleic acid amplification test.	Strong
Initially prescribe a single antibiotic or a combination of two antibiotics active against *Chlamydia trachomatis* and *Enterobacterales* in young sexually active men; in older men without sexual risk factors only *Enterobacterales* have to be considered.	Strong
If gonorrhoeal infection is likely give single dose ceftriaxone 1000 mg intramuscularly or intravenously* in addition to a course of an antibiotic active against *Chlamydia trachomatis*.	Strong
Adjust antibiotic agent when pathogen has been identified and adjust duration according to clinical response.	Weak
Follow national policies on reporting and tracing/treatment of contacts for sexually transmitted infections.	Strong

**Despite the lack of RCTs there is increasing evidence that intravenous treatment with ceftriaxone is safe and effective for the treatment of gonorrhoeal infections and avoids the discomfort of an intramuscular injection for patients [316].*

Figure 2: Diagnostic and treatment algorithm for men with acute epididymitis


Acute scrotal pain, and swelling in adult male
Torsion suspected
Suspected epididymitis
Urgent surgical exploration
Gonorrhoea unlikely
Gonorrhoea likely
Mid-stream urine for culture
Urethral swab/smear
First-voided urine for nucleic acid amplification test
Failure to respond or abscess present
Scrotal ultrasound examination Clinical assesment
Single antibiotic or a combination of two antibiotics active against Chlamydia trachomatis and Enterobacterales
Consider parenteral therapy if severe infection
Ceftriaxone 1000mg i.m. or i.v.* plus a course of an antibiotic active against Chlamydia trachomatis
Proven sexually transmitted infection
• Reporting
• Check cure
• Trace and treat contacts

i.m. = intramuscular; i.v. intravenously.
** Despite the lack of RCTs there is increasing evidence that intravenous treatment with ceftriaxone is safe and effective for the treatment of gonorrhoeal infections and avoids the discomfort of an intramuscular injection for patients [316].*

3.13 Fournier's Gangrene (Necrotising fasciitis of the perineum and external genitalia)

3.13.1 Epidemiology, Aetiology and Pathophysiology

Fournier's gangrene is an aggressive and frequently fatal polymicrobial soft tissue infection of the perineum, peri-anal region, and external genitalia [383]. It is an anatomical sub-category of necrotising fasciitis with which it shares a common aetiology and management pathway.

3.13.2 Diagnostic Evaluation

Typically, there is painful swelling of the scrotum or perineum with sepsis [383]. Examination shows small necrotic areas of skin with surrounding erythema and oedema. Crepitus on palpation and a foul-smelling exudate occurs with more advanced disease. Patient risk factors for occurrence and mortality include being immunocompromised, most commonly diabetes or malnutrition, recent urethral or perineal surgery, and high body mass index (BMI). In up to 40% of cases, the onset is more insidious with undiagnosed pain often resulting in delayed treatment [384]. A high index of suspicion and careful examination, particularly of obese patients, is required. Computed tomography or MRI can help define para-rectal involvement, suggesting the need for bowel diversion [383].

3.13.3 Disease Management

The degree of internal necrosis is usually vastly greater than suggested by external signs, and consequently, adequate, repeated surgical debridement with urinary diversion by suprapubic catheter is necessary to reduce mortality [383]. Consensus from case series suggests that surgical debridement should be early (< 24 hours) and complete, as delayed and/or inadequate surgery may result in higher mortality [383]. Immediate empiric

parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue. A suggested regime would comprise a broad-spectrum penicillin or third-generation cephalosporin, gentamicin and metronidazole or clindamycin [383]. This can then be refined, guided by microbiological culture.

*3.13.4 **Evidence Summary***

A systematic literature search from 1980 to July 2017 was performed. From 640 references one RCT [385], two systematic reviews [386, 387], one narrative review [383], three registry studies [388-390], one prospective cohort study [391] and two retrospective comparative cohort studies with at least 25 patients [392, 393] were selected. The three registry studies from the United States [388-390], found mortality rates of 10%, 7.5% and 5% from 650, 1,641 and 9,249 cases, respectively. Older age, diabetes and high BMI were associated with higher risk. A prospective cohort study showed that disease-specific severity scores did predict outcome, but were not superior to generic scoring systems for critical care [391]. The evidence questions addressed were:

1. What is the best antimicrobial treatment strategy to reduce mortality?
2. What is the best debridement and reconstruction strategy to reduce mortality and aid recovery?
3. Are there any effective adjuvant treatments that improve outcome?

Concerning the evidence questions:

A. A low quality retrospective case series [392] with 168 patients found no significant difference in mortality between patients given ≤ 10 days of parenteral antibiotics (80 patients) and those given > 10 days (88 patients).

B. A systematic review of wound closure techniques [387] found low-quality evidence from 16 case series involving 425 male patients. They recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.

C. A systematic review on the use of hyperbaric oxygen therapy [386] included three comparative case series and four other case series. All were retrospective and published prior to 2000. No consistent evidence of benefit was found; an RCT was advised. A more recent comparative case series [393] suggested benefit for use of hyperbaric oxygen therapy in sixteen patients compared to twelve cases without use of such therapy in terms of reduced mortality and fewer debridements (low quality evidence). A low-quality RCT [385] with 30 patients found that use of honey soaked dressings resulted in a shorter hospital stay (28 vs. 32 days) than dressing soaked with Edinburgh solution of lime (EUSOL). No evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene was found.

*3.13.5 **Summary of evidence and recommendations for the disease management of Fournier's Gangrene***

Summary of evidence	**LE**
Immediate empiric parenteral antibiotic treatment should be given that covers all probable causative organisms and can penetrate inflammatory tissue.	3
A systematic review of wound closure techniques recommended primary or secondary wound closure for scrotal defects ≤ 50% with the use of flaps or skin grafts for defects involving > 50% of the scrotum or with extension outside the scrotum.	3
No consistent evidence of benefit for hyperbaric oxygen therapy was found.	3
A low quality RCT found that dressings soaked in honey resulted in a shorter hospital stay than dressing soaked with EUSOL.	3
No evidence of benefit for use of negative-pressure (vacuum) wound therapy in Fournier's gangrene was found.	4

Recommendations	**Strength rating**
Start treatment for Fournier's gangrene with broad-spectrum antibiotics on presentation, with subsequent refinement according to culture and clinical response.	Strong
Commence repeated surgical debridement for Fournier's gangrene within 24 hours of presentation.	Strong
Do not use adjunctive treatments for Fournier's gangrene except in the context of clinical trials.	Weak

Table 11: Suggested regimens for antimicrobial therapy for Fournier's Gangrene of mixed microbiological aetiology adapted from [394]**.**

Antimicrobial	Dosage
Piperacillin-tazobactam plus Vancomycin	4.5 g every 6-8 h IV 15 mg/kg every 12 h
Imipenem-cilastatin	1 g every 6-8 h IV
Meropenem	1 g every 8 h IV
Ertapenem	1 g once daily
Gentamicin	5 mg/kg daily
Cefotaxime plus metronidazole or clindamycin	2 g every 6 h IV 500 mg every 6 h IV 600-900 mg every 8 h IV
Cefotaxime plus fosfomycin plus metronidazole	2 g every 6 h IV 5 g every 8 h IV 500 mg every 6 h IV

IV = intravenous.

3.14 Management of Human papilloma virus in men

*3.14.1 **Epidemiology***

Human papilloma virus (HPV) is one of the most frequently sexually transmitted viruses encompassing both oncogenic (low- and high-risk variants) and non-oncogenic viruses. HPV16 is the most common oncogenic variant, detected in 20% of all HPV cases [395]. A recent meta-analysis revealed a prevalence of 49% of any type of HPV and 35% of high-risk HPV in men [396]. Similar to the female genital tract, half of all HPV infections in the male genital tract are co-infections (≥ 2 HPV strains) [397].

HPV presence is dependent on study setting. In men attending urological clinics HPV was detected in 6% of urine samples [398]. A meta-analysis reported seminal HPV in 4.5-15.2% of patients resulting in seminal HPV being associated with decreased male fertility [395]. A cross sectional study of 430 men presenting for fertility treatment detected HPV in 14.9% of semen samples [399]. The presence of HPV in semen was not associated with impaired semen quality [399]. However, another systematic review reported a possible association between HPV and altered semen parameters, and in women possible miscarriage or premature rupture of the membrane during pregnancy [400]. HPV6 and/or 11 were the most common genotypes detected in an observational study of anogenital warts, whilst HPV16 is correlated with severity of anal cytology [401]. The incidence of non-oncogenic HPV infection has been shown to be higher in men than women [402]. In males, approximately 33% of penile cancers and up to 90% of anal cancers are attributed to high-risk HPV infections, primarily with HPV16 [403]. The EAU Penial Cancer Guidelines will publish a comprehensive update in March 2022 including the results of two systematic reviews on HPV and penile cancer. Oral HPV is associated with oropharyngeal carcinomas approximately 22.4%, 4.4% and 3.5% of oral cavity, oropharynx and larynx cancers, respectively are attributed to HPV [403]. Systematic reviews have reported prevalence rates of oral HPV from 5.5-7.7%, with HPV16 present in 1-1.4% of patients [404, 405].

*3.14.2 **Risk factors***

Risk factors for HPV infection include early age of first sexual intercourse, sexual promiscuity, higher frequency of sexual intercourse, smoking and poor immune function [406-410]. Incidence and prevalence of overall HPV was considerably higher in men who have sex with men (MSM) compared to heterosexuals [404, 407]. Overall, the prevalence of HPV in different sites seems to be higher in young, sexual-active adults compared to other population groups [406]. Stable sexual habits, circumcision and condom use are protective factors against HPV [396, 410-414]. Added risk factors of oral HPV infection are alcohol consumption, poor oral hygiene and sexual behaviours (oral and vaginal) [404, 406]. Positive HIV status, phimosis, and HPV status of the partner have also been associated with anogenital HPV status and decreased clearance in a number of studies [411].

*3.14.3 **Transmission***

HPV typically spreads by sustained direct skin-to-skin or mucosal contact, with vaginal, oral and anal sex being the most common transmission route [408]. In addition, HPV has been found on surfaces in medical settings and public environments raising the possibility of object-to-skin/mucosa transmission [415]. Further studies on non-sexual and non-penetrative sexual transmission are needed to understand the complexity of HPV transmission. HPV transmission may also be influenced by genotype, with a higher incidence of HPV51 and HPV52 and a high prevalence of HPV16 and HPV18 in the general and high-risk male population [408].

3.14.4 ***Clearance***

HPV time-to-clearance ranges from 1.3 to 42.1 months [416]. Clearance may be influenced by HPV genotype, patients' characteristics and affected body site [407, 411, 416]. HPV16 has the highest incidence of high-risk HPV variants and has the lowest clearance across sites [411].

3.14.5 ***Diagnosis***

There is currently no approved test for HPV in men. Routine testing to check for HPV or HPV-related disease in men is not recommended. A physical examination to identify HPV lesions should be carried out. An acetic acid test to diagnose sub-clinical HPV lesions may be performed. If the diagnosis is uncertain or there is a suspicion of cancer a biopsy should be carried out. Intra-urethral condylomas are relatively uncommon and are usually limited to the distal urethral meatus [417, 418]. Urethrocystoscopy may be used to diagnose the presence of intra-urethral or bladder warts [418]; however, there is no high-level evidence for the use of invasive diagnostic tools for localisation of intra-urethral HPV. For detailed recommendations on the diagnosis of anogenital warts please refer to the IUSTI-European guideline for the management of anogenital warts [419].

3.14.6 ***Treatment of HPV related diseases***

Approximately 90% of HPV infections do not cause any problems and are cleared by the body within two years. However, treatment is required when HPV infection manifests as anogenital warts to prevent the transmission of HPV-associated anogenital infection and to minimise the discomfort caused to patients [419]. Of the treatment options available only surgical treatment has a primary clearance rate approaching 100%.

3.14.6.1 Treatments suitable for self-application

Patient-applied treatments include podophyllotoxin, salicylic acid, imiquimod, polyphenon E, 5-fluoracil and potassium hydroxide [419]. Imiquimod 5% cream showed a total clearance of external genital or perianal warts in 50% of immunocompetent patients [420] as well as in HIV positive patients successfully treated with highly active antiretroviral therapy [421]. A Cochrane review of published RCTs found imiquimod to be superior to placebo in achieving complete clearance of warts (RR: 4.03, 95% CI: 2.03–7.99) [422]. The recommended treatment schedule is imiquimod 5% cream applied to all external warts overnight three times each week for sixteen weeks [419]. In an RCT involving 502 patients with genital and/or perianal warts sinecatechins 15% and 10% showed a complete clearance of all baseline and newly occurring warts in 57.2% and 56.3% of patients, respectively vs. 33.7% for placebo [423]. In addition, sinecatechins 10% has been shown to be associated with lower short-term recurrence rates when used as sequential therapy after laser CO_2 ablative therapy [424]. Sinecatechins is applied three times daily until complete clearance, or for up to sixteen weeks. Clearance rates of 36–83% for podophyllotoxin solution and 43–70% for podophyllotoxin cream have been reported [419]. A systematic review and meta-analysis confirmed the effectiveness of podophyllotoxin 0.5% solution relative to placebo (RR: 19.86, 95% CI: 3.88–101.65) [425]. Podophyllotoxin is self-applied to lesions twice daily for three days, followed by four rest days, for up to four or five weeks. An RCT has also shown potassium hydroxide 5% to be an effective, safe, and low-cost treatment modality for genital warts in men [426].

3.14.6.2 Physician-administered treatment

Physician-administered treatments included cryotherapy (79-88% clearance rate; 25-39% recurrence rate), surgical treatment (61-94% clearance rate), including excision, electrosurgery, electrocautery and laser therapy (75% clearance rate) [427, 428]. Physician-administered therapies are associated with close to 100% clearance rates, but they are also associated with high rates of recurrence as they often fail to eliminate invisible HPV-infected lesions [427, 428]. No data about the superiority of one treatment over another are available. However, among all interventions evaluated in a recent systematic review and network meta-analysis, surgical excision appeared to be the most effective treatment at minimising risk of recurrence [429].

3.14.6.3 Summary of evidence and recommendations for the treatment of anogenital warts

Summary of evidence	**LE**
A Cochrane review of published RCTs found imiquimod to be superior to placebo in achieving complete clearance of warts.	1b
In an RCT sinecatechins 15% and 10% showed a complete clearance of all baseline and newly occurring warts in 57.2% and 56.3% of patients, respectively vs. 33.7% for placebo.	1b
A systematic review and meta-analysis confirmed the effectiveness of podophyllotoxin 0.5% solution relative to placebo.	1b
A systematic review and meta-analysis reported that among all physician-applied therapy, surgical excision seemed to be the most effective at minimising risk of recurrence.	1a

Recommendations	Strength rating
Use self-administered imiquimd 5% cream applied to all external warts overnight three times each week for sixteen weeks for the treatment of anogenital warts.	Strong
Use self-administered sinecatechins 15% or 10% applied to all external warts three times daily until complete clearance, or for up to sixteen weeks for the treatment of anogenital warts.	Strong
Use self-administered podophyllotoxin 0.5% self-applied to lesions twice daily for three days, followed by four rest days, for up to four or five weeks for the treatment of anogenital warts.	Strong
Use cryotherapy or surgical treatment (excision, electrosurgery, electrocautery and laser therapy) to treat anogenital warts based on an informed discussion with the patient.	Strong

*3.14.7 **Circumcision for reduction of HPV prevalence***

Male circumcision is a simple surgical procedure which has been shown to reduce the incidence of sexually transmitted infections including HIV, syphilis and HSV-2 [430]. Two systematic reviews and meta-analyses, showed an inverse association between male circumcision and genital HPV prevalence in men [414, 416]. It has been suggested that male circumcision could be considered as an additional one-time preventative intervention likely to reduce the burden of HPV-related diseases in both men and women, particularly among those countries in which HPV vaccination programs and cervical screening are not available [416].

Summary of evidence	LE
Two systematic reviews and meta-analyses, showed an inverse association between male circumcision and genital HPV prevalence in men.	1a

Recommendation	Strength rating
Discuss male circumcision with patients as an additional one-time preventative intervention for HPV-related diseases.	Strong

*3.14.8 **Therapeutic vaccination***

Three different vaccines against HPV have been licensed to date, but routine vaccination of males is currently implemented in only a few countries including Australia, Canada, the USA and Austria. The aim of male vaccination is to reduce the rate of anal and penile cancers as well as head and neck cancers [403, 431].

A systematic review including a total of 5,294 patients reported vaccine efficacy against persisting (at least six months) anogenital HPV16 infections of 46.9% (28.6-60.8%) and against persisting oral infections of 88% (2–98%). A vaccine efficacy of 61.9% (21.4–82.8%) and 46.8% (20-77.9%) was observed against anal intraepithelial neoplasia grade 2 and 3 lesions, respectively [403]. The systematic review reported no meaningful estimates on vaccine efficacy against penile intraepithelial neoplasia grade 2 or 3, and no data were identified for anal, penile or head and neck squamous cell cancers [403].

A phase 3 clinical trial including 180 male patients evaluated the potential of MVA E2 recombinant vaccinia virus to treat intraepithelial lesions associated with papillomavirus infection [432]. The study showed promising results in terms of immune system stimulation against HPV lesions as well as regression in intraepithelial lesions.

Summary of evidence	LE
The role of therapeutic HPV vaccination in males in terms of effectiveness and safety is limited by the small number of relevant studies.	2
Therapeutic HPV vaccination in males is moderately effective against persistent anogenital HPV16 infection [(46.9% (28.6-60.8%)] and high-grade anal intraepithelial lesions [grade 2: 61.9% (21.4–82.8%); grade 3: 46.8% (20-77.9%)].	1b

Recommendation	Strength rating
Offer HPV vaccine to males after surgical removal of high-grade anal intraepithelial neoplasia.	Weak

*3.14.9 **Prophylactic vaccination***

A systematic review and meta-analysis reported that vaccination is moderately effective against genital HPV-related diseases irrespective of an individual's HPV status; however, higher vaccine efficacy was observed in HPV-naïve males [403]. Supporting the early vaccination of boys with the goal of establishing optimal vaccine-

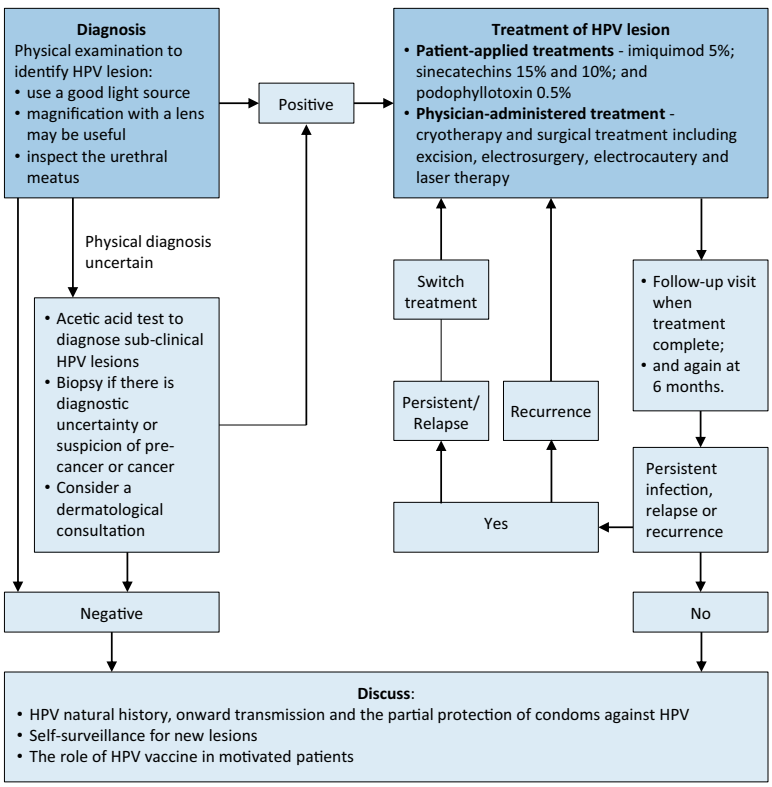
induced protection before the onset of sexual activity [403]. An RCT including 1,124 patients demonstrated high efficacy of the quadrivalent HPV vaccine vs. placebo against HPV6/11/16/18-related persistent infections [433]. Furthermore, the vaccine elicited a robust immune response and was well tolerated with mild vaccination-related adverse events e.g. injection-site pain and swelling [433]. In addition, a Cochrane review, demonstrated that the quadrivalent HPV vaccine appears to be effective in the prevention of external genital lesions and genital warts in males [434].

Despite the fact quadrivalent HPV vaccines were approved for use in young adult males in 2010 vaccination rates have remained low at 10-15% [435]. Barriers to uptake in this patient group include lack of awareness about HPV vaccines and HPV-related diseases, concerns about vaccine safety and efficacy, economic/cost issues related to vaccine uptake, underestimation of HPV infection risks and sexual activity [435]. Healthcare professionals should provide easily understood and accessible communication resources regarding these issues, in order to educate young adult males and their families on the importance of HPV vaccination to reduce the incidence of certain cancers in later life [435, 436].

Summary of evidence	LE
HPV vaccine is effective in the prevention of external genital lesions and genital warts in males.	1a
HPV vaccination is moderately effective against genital HPV-related diseases irrespective of a individuals HPV status; however, higher vaccine efficacy was observed in HPV-naïve males.	1a
A systematic review of HPV vaccination barriers among adolescent and young adult males identified a number of barriers to vaccine uptake including fear of side-effects, limited HPV awareness, financial costs and changes in sexual activity.	1b
An intervention study to evaluate whether electronic messaging can increase HPV vaccine completion and knowledge among college students concluded that intervention increased knowledge, but not vaccine completion.	2b

Recommendations	Strength rating
Offer early HPV vaccination to boys with the goal of establishing optimal vaccine-induced protection before the onset of sexual activity.	Strong
Apply diverse communication strategies in order to improve HPV vaccination knowledge in young adult males.	Strong

Figure 3: Diagnostic and treatment algorithm for the management of HPV in men


Diagnosis
Physical examination to identify HPV lesion:
• use a good light source
• magnification with a lens may be useful
• inspect the urethral meatus
Positive
Treatment of HPV lesion
• Patient-applied treatments - imiquimod 5%; sinecatechins 15% and 10%; and podophyllotoxin 0.5%
• Physician-administered treatment - cryotherapy and surgical treatment including excision, electrosurgery, electrocautery and laser therapy
Physical diagnosis uncertain
• Acetic acid test to diagnose sub-clinical HPV lesions
• Biopsy if there is diagnostic uncertainty or suspicion of pre-cancer or cancer
• Consider a dermatological consultation
Switch treatment
Persistent/ Relapse
Recurrence
• Follow-up visit when treatment complete;
• and again at 6 months.
Persistent infection, relapse or recurrence
Yes
No
Negative
Discuss:
• HPV natural history, onward transmission and the partial protection of condoms against HPV
• Self-surveillance for new lesions
• The role of HPV vaccine in motivated patients

3.15 Peri-Procedural Antibiotic Prophylaxis

3.15.1 ***General Principles***

3.15.1.1 Definition of infectious complications

The European Centre for Disease Prevention and Control (ECDC) and the CDC have both presented similar definitions recommended for the evaluation of infectious complications [437, 438].

3.15.1.2 Non-antibiotic measures for asepsis

There are a number of non-antibiotic measures designed to reduce the risk of surgical site infection (SSI), many are historically part of the routine of surgery. The effectiveness of measures tested by RCTs are summarised in systematic reviews conducted by the Cochrane Wounds Group (http://wounds.cochrane.org/news/reviews). Urological surgeons and the institutions in which they work should consider and monitor maintenance of an aseptic environment to reduce risk of infection from pathogens within patients (microbiome) and from outside the patient (nosocomial/healthcare-associated). This should include use of correct methods of instrument cleaning and sterilisation, frequent and thorough cleaning of operating rooms and recovery areas and thorough disinfection of any contamination. The surgical team should prepare to perform surgery by effective hand washing [439], donning of appropriate protective clothing and maintenance of asepsis. These measures should continue as required in recovery and ward areas.

Patients should be encouraged to shower pre-operatively, but use of chlorhexidine soap does not appear to be beneficial [440]. Although evidence quality is low, any required hair removal appears best done by clipping, rather than shaving, just prior to incision [441]. Mechanical bowel preparation should not be used as evidence review suggests harm not benefit [442, 443]. There is some weak evidence that skin preparation using alcoholic solutions or chlorhexidine result in a lower rate of SSI than iodine solutions [444]. Studies on the use of plastic adherent drapes showed no evidence of benefit in reducing SSI [445].

3.15.1.3 Detection of bacteriuria prior to urological procedures

Identifying bacteriuria prior to diagnostic and therapeutic procedures aims to reduce the risk of infectious complications by controlling any pre-operative detected bacteriuria and to optimise antimicrobial coverage in conjunction with the procedure. A systematic review of the evidence identified eighteen studies comparing the diagnostic accuracy of different index tests (dipstick, automated microscopy, dipslide culture and flow cytometry), with urine culture as the reference standard [446]. The systematic review concluded that none of the alternative urinary investigations for the diagnosis of bacteriuria in adult patients prior to urological interventions can currently be recommended as an alternative to urine culture [446].

3.15.1.4 Choice of agent

Urologists should have knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence in order to establish written local guidelines. These guidelines should cover the five modalities identified by the ECDC following a systematic review of the literature [447]. The agent should ideally not be one that may be required for treatment of infection. When risk of skin wound infection is low or absent, an aminoglycoside (gentamicin) should provide cover against likely uropathogens provided the eGFR is > 20 mL/min; second generation cephalosporins are an alternative [448]. Recent urine culture results including presence of any multi-resistant organisms, drug allergy, history of *C. difficile* associated diarrhoea, recent antibiotic exposure, evidence of symptomatic infection pre-procedure and serum creatinine should be checked. The panel have decided not to make recommendations for specific agents for particular procedures as there is considerable variation in Europe and worldwide regarding bacterial pathogens, their susceptibility and availability of antibiotic agents.

3.15.2 ***Specific procedures and evidence question***

An updated literature search from February 2017 (cut-off of last update) to June 2021 identified RCTs, systematic reviews and meta-analyses that investigated the benefits and harms of using antibiotic prophylaxis prior to specific urological procedures. The available evidence enabled the panel to make recommendations concerning urodynamics, cystoscopy, stone procedures (extracorporeal shockwave lithotripsy [ESWL], ureteroscopy and percutaneous nephrolithotomy [PCNL]), transurethral resection of the prostate (TURP) and transurethral resection of the bladder (TURB). For nephrectomy and prostatectomy the scientific evidence was too weak to allow the panel to make recommendations either for or against antibiotic prophylaxis. The general evidence question was: Does antibiotic prophylaxis reduce the rate of post-operative symptomatic UTI in patients undergoing each named procedure?

3.15.2.1 Urodynamics

The literature search identified one systematic review for antibiotic prophylaxis in women only [449]. This included three RCTs (n=325) with the authors reporting that prophylactic antibiotics reduced the risk of

bacteriuria but not clinical UTI after urodynamics [449]. A previous Cochrane review identified nine RCTs enrolling 973 patients with overall low quality and high or unclear risks of bias [450]. The outcome of clinical UTI was reported in four trials with no benefit found for antibiotic prophylaxis vs. placebo [RR (95%CI) 0.73 (0.52-1.03)]. A meta-analysis of nine trials showed that use of antibiotics reduced the rate of post-procedural bacteriuria [RR (95%CI) 0.35 (0.22-0.56)] [450].

3.15.2.2 Cystoscopy

Three systematic reviews and meta-analyses [451-453] and one additional RCT [454] on cystoscopy for stent removal were identified. Garcia-Perdomo *et al*., included seven RCTs with a total of 3,038 participants. The outcome of symptomatic UTI was measured by five trials of moderate overall quality and meta-analysis showed a benefit for using antibiotic prophylaxis [RR (95%CI) 0.53 (0.31 – 0.90)]; ARR 1.3% (from 2.8% to 1.5%) with a NNT of 74 [452]. This benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis. Carey *et al*., included seven RCTs with 5,107 participants. Six trials were included in meta-analysis of the outcome of symptomatic bacteriuria which found benefit for use of antibiotic prophylaxis [RR (95%CI) 0.34 (0.27 – 0.47)]; ARR 3.4% (from 6% to 2.6%) with NNT of 28 [451]. Zeng *et al*., included twenty RCTs and two quasi-RCTs with a total of 7,711 participants. The outcome of symptomatic UTI was measured by eleven RCTs of low overall quality and meta-analysis showed a possible benefit for using antibiotic prophylaxis [RR (95% CI) 0.49 (0.28 – 0.86)] [453]. For systemic UTI, antibiotic prophylaxis showed no effect compared with placebo or no treatment in five RCTs [RR (95% CI) 1.12 (0.38 - 3.32)]. However, prophylactic antibiotics may increase bacterial resistance [(RR (95% CI) 1.73 (1.04 – 2.87)].

Given the low absolute risk of post-procedural UTI in well-resourced countries, the high number of procedures being performed, and the high risk of contributing to increasing antimicrobial resistance the panel consensus was to strongly recommend not to use antibiotic prophylaxis in patients undergoing urethrocystoscopy (flexible or rigid).

3.15.2.3 Interventions for urinary stone treatment

3.15.2.3.1 Extracorporeal shockwave lithotripsy

For patients without bacteriuria undergoing ESWL two systematic reviews and meta-analyses were identified with latest search dates of November 2011 and October 2012, respectively [455, 456] and one further RCT [457]. Lu *et al*., included nine RCTs with a total of 1,364 patients and found no evidence of benefit in terms of reducing the rate of post-procedural fever or bacteriuria [455]. Mrkobrada *et al*., included eight RCTs with a total of 940 participants and found no evidence of benefit for antibiotic prophylaxis to reduce rate of fever or trial-defined infection [456]. A RCT with 274 patients and severe risk of bias found no reduction in fever at up to one week post-procedure using a single dose of levofloxacin 500 mg and no difference in the rate of bacteriuria [457]. Another RCT (n=600) again with severe risk of bias found no difference in UTI and positive urine culture rates at two weeks post-procedure using 200 mg ofloxacin post-operatively for three-days vs. placebo [457a].

For patients with bacteriuria or deemed at high risk of complications one RCT comparing the use of ofloxacin or trimethoprim-sulphamethoxazole for three days prior and four days subsequent to ESWL in 56 patients with ureteric stents was identified [458]. They found no difference in rate of clinical UTI at seven days (no events) and no difference in post-ESWL bacteriuria.

3.15.2.3.2 Ureteroscopy

One updated systematic review and meta-analysis with last search date of June 2017 was identified and included eleven RCTs with 4,591 patients [459]. The meta-analysis found that post-operative pyuria and bacteriuria rates were significantly lower in patients who received pre-operative antibiotic prophylaxis pyuria (OR: 0.42, 95% CI 0.25–0.69 and OR: 0.25, 95% CI 0.11–0.58, respectively). Five studies assessed post-operative febrile UTI (fUTI) and found no difference in the rate of fUTIs between patients who did or did not receive antibiotic prophylaxis (OR: 0.82, 95% CI 0.40– 1.67). However, a significantly higher risk of post-operative fever in the pre-operative antibiotic prophylaxis group (OR: 1.75, 95% CI 1.22–2.50) was reported. A subgroup analysis on the type of pre-operative antibiotic prophylaxis found no difference between a single dose of oral vs. intravenous antibiotics [459].

A RCT comparing different ciprofloxacin-based antibiotic prophylaxis regimens on the incidence of SIRS after URS found there was no difference in the incidences of SIRS between the regimens including the zero dose regime [460]. However, there was a greater risk of SIRS in patients who did not received antibiotic prophylaxis when the stone size was > 200 mm^2 [460]. Another RCT comparing the use of two oral doses of 3 g fosfomycine tromethamine before surgery to standard of care did not find any difference in the incidence of infections, bacteriuria or fever [461].

Panel discussion considered that despite low-quality evidence suggesting no benefit in reducing risk of clinical UTI, clinicians and patients would prefer to use prophylaxis to prevent kidney infection or sepsis. Ideally this should be examined in a robustly designed clinical study.

3.15.2.3.3 Percutaneous neprolithotomy (PNL)

The largest systematic review and meta-analysis performed, latest search date April 2019, included 1,549 patients in thirteen comparative studies on antibiotic prophylaxis strategies for PNL [462]. Compared with a single dose before surgery pre-operative antibiotic prophylaxis significantly reduced post-operative sepsis and fever (OR 0.31, 95%CI 0.20-0.50 and OR 0.26, 95%CI 0.14-0.48, respectively) [462]. Similarly, the rate of positive pelvic urine and positive stones culture were reduced when pre-operative prophylaxis was given. There was no difference in sepsis rates between patients receiving or not receiving post-operative prophylaxis; however, patients who received post-operative antibiotic prophylaxis had more fever [462].

Four RCTs with overall low risk of bias comparing different antibiotic regimes in PNL were identified [463-466]. Seyrek *et al*., compared the rate of SIRS following PNL in 191 patients receiving either a combination of sulbactam/ampicillin or cefuroxime. There was no difference in SIRS or urosepsis rates [463]. Tuzel *et al*., investigated single dose ceftriaxone vs. ceftriaxone and subsequently an oral third-generation cephalosporin until after nephrostomy catheter withdrawal at mean of three days in 73 participants undergoing PNL. They found no difference in rate of infectious complications between the two antibiotic regimens [464]. Taken *et al*., compared the administration of 1 g ceftriaxone and 1 g cefazoline both administered 30 minutes before surgery and continued till nephrostomy removal. They found no difference in terms of SRIS or sepsis between groups [466]. *Omar et al*., compared ciprofloxacin 200 mg i.v. vs. 2 mg cefotaxime 30 minutes before and 12 hours after surgery and found a higher rate of fever in the cefotaxime group [465]. However, these results remain limited by the high risk of bias and the lack of data regarding post-operative infection. These studies give moderate evidence that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.

3.15.2.4 Transurethral resection of the prostate

A systematic review of 39 RCTs with search date up to 2009 was identified [467]. The update search to February 2017 did not reveal any further relevant studies. Of the 39 RCTs reviewed by Dahm *et al*., six trials involving 1,666 men addressed the risk of septic episodes, seventeen trials reported procedure related fever and 39 investigated bacteriuria. Use of prophylactic antibiotics compared to placebo showed a relative risk reduction (95% CI) for septic episode of 0.51 (0.27-0.96) with ARR of 2% (3.4% - 1.4%) and a NNT of 50. The risk reduction (95% CI) for fever was 0.64 (0.55-0.75) and 0.37 (0.32-0.41) for bacteriuria.

3.15.2.5 Transurethral resection of the bladder

One systematic review which included seven trials with a total of 1,725 participants was identified [468]. Antimicrobial prophylaxis showed no significant effect on post-operative UTIs [OR (95% CI) 1.55 (0.73 - 3.31)] and asymptomatic bacteriuria [OR (95% CI) 0.43 (0.18 – 1.04)] [468]. The review did not attempt sub-group analysis according to presence of risk factors for post-operative infection such as tumour size. Risk factors for development of post-operative UTIs were evaluated only by three of the included studies and most of the parameters were analysed by no more than one study.

A RCT (n=100) comparing oral fosfomycin 3 g (the night before surgery) vs. intravenous cefoxitin 2 g (30 minutes pre- and 24 hours post-surgery) on post-operative UTIs found that a single oral administration of fosfomycin was non-inferior to intravenous administration of cefoxitin in the prevention of post-TURB UTI, even in patients considered at higher risk [469].

Panel discussion concluded that a weak recommendation to use antibiotic prophylaxis for patients undergoing TURB who had a high risk of suffering post-operative sepsis would be appropriate.

3.15.2.6 Midurethral slings

One systematic review and meta-analysis identified one study assessing the role of pre-operative antibiotics for midurethral sling surgery alone [470]. The study was halted due to low rate of infectious outcomes seen at the first scheduled interim analysis. The study enrolled 29 women in the antibiotic prophylaxis (cefazolin) group and 30 in the placebo group with a total follow-up of six months. No statistically significant difference between the cefazolin and placebo groups, with respect to wound infections [1 (3.3%) vs. 0 (0%)] or bacteriuria [3 (10%) vs. 1 (3.5%)] was found [470].

3.15.2.7 Renal tumour ablation

One systematic review publication date 2018 included 6,952 patients across 51 studies [471]. Infectious complications were reported in 74 patients including fever (60.8%), abscess (21.6%) and UTI (8.1%). Prophylactic antibiotic use was reported in 5.4% of patients, but it was not possible to study its association to infectious complications due to lack of reporting.

3.15.2.8 Prostate biopsy

3.15.2.8.1 Transperineal prostate biopsy

A total of seven randomised studies including 1,330 patients compared the impact of biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (37 events among 657 men) compared to transperineal biopsy (22 events among 673 men), [RR (95% CIs) 1.81 (1.09 to 3.00)] [472]. In addition, a systematic review including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [473]. Finally, a population-based study from the UK (n=73,630) showed lower re-admission rates for sepsis in patients who had transperineal vs. transrectal biopsies (1.0% vs. 1.4%, respectively) [474]. The available evidence demonstrates that the transrectal approach should be abandoned in favour of the transperineal approach despite any possible logistical challenges. To date, no RCT has been published investigating different antibiotic prophylaxis regimens for transperineal prostate biopsy.

3.15.2.8.2 Transrectal prostate biopsy

Meta-analysis of eight RCTs including 1,786 men showed that use of a rectal povidone-iodine preparation before biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications [RR (95% CIs) 0.55 (0.41 to 0.72)] [472]. Single RCTs showed no evidence of benefit for perineal skin disinfection [475], but reported an advantage for rectal povidone-iodine preparation before biopsy compared to after biopsy [476].

A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications [RR (95% CIs) 0.96 (0.64 to 1.54)] [472].

A meta-analysis of 26 RCTs with 3,857 patients found no evidence that use of peri-prostatic injection of local anaesthesia resulted in more infectious complications than no injection [RR (95% CIs) 1.07 (0.77 to 1.48)] [472]. A meta-analysis of nine RCTs including 2,230 patients found that extended biopsy templates showed comparable infectious complications to standard templates [RR (95% CIs) 0.80 (0.53 to 1.22)] [472]. Additional meta-analyses found no difference in infections complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. non-coaxial), needle size (large vs. small), and number of injections for peri-prostatic nerve block (standard vs. extended) [472].

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control [RR (95% CIs) 0.56 (0.40 to 0.77)] [477].

Fluoroquinolones have been traditionally used for antibiotic prophylaxis in this setting; however, overuse and misuse of fluoroquinolones has resulted in an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones resulting in the suspension of the indication for peri-operative antibiotic prophylaxis including prostate biopsy [121].

A systematic review and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that in countries where fluoroquinolones are allowed as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, or augmented prophylaxis (combination of two or more different classes of antibiotics) is recommended [477]. In countries where use of fluoroquinolones are suspended cephalosporins or aminoglycosides can be used as individual agents with comparable infectious complications based on meta-analysis of two RCTs [477]. A meta-analysis of three RCTs reported that fosfomycin trometamol was superior to fluoroquinolones [RR (95% CIs) 0.49 (0.27 to 0.87)] [477], but routine general use should be critically assessed due to the relevant infectious complications reported in non-randomised studies [478]. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swap/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See figure 4 for prostate biopsy workflow to reduce infections complications.

*3.15.3 **Summary of evidence and recommendations for peri-procedural antibiotic prophylaxis***

Summary of evidence	**LE**
The outcome of clinical UTI was reported in four out of eleven RCTs with no benefit found for antibiotic prophylaxis vs. placebo in patients following filling and voiding cystometry.	1b
A meta-analysis of five trials of moderate quality showed a benefit for using antibiotic prophylaxis for the reduction of symptomatic UTI in patients undergoing cystoscopy. However, this benefit was not seen if only the two trials with low risk of bias were used in the meta-analysis.	1a

Two meta-analyses found no benefit for antibiotic prophylaxis following ESWL in terms of reducing the rate of post-procedural fever and bacteriuria or trial-defined infection in patients without bacteriuria.	1a
Two meta-analyses found no evidence of benefit for antibiotic prophylaxis prior to ureteroscopy in reducing the rate of clinical UTI; however, the rate of bacteriuria was reduced.	1a
A meta-analysis of five RCTs demonstrated a moderate level of evidence that antibiotic prophylaxis was associated with a statistically significant reduction in the risk of post-procedural UTI following PNL.	1a
Two RCTs concluded that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.	1b
A systematic review of 39 RCTs concluded that antibiotic prophylaxis reduced the rate of infectious complications in men undergoing TURP.	1b
A systematic review of two RCTs found no benefit for antibiotic prophylaxis in patients undergoing TURB.	1b
A meta-analysis of seven studies including 1,330 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
A meta-analysis of eight RCTs including 1,786 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

Recommendations	**Strength rating**
Do not use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following: • urodynamics; • cystoscopy; • extracorporeal shockwave lithotripsy.	Strong
Use antibiotic prophylaxis to reduce the rate of symptomatic urinary infection following ureteroscopy.	Weak
Use single dose antibiotic prophylaxis to reduce the rate of clinical urinary infection following percutaneous nephrolithotomy.	Strong
Use antibiotic prophylaxis to reduce infectious complications in men undergoing transurethral resection of the prostate.	Strong
Use antibiotic prophylaxis to reduce infectious complications in high-risk patients undergoing transurethral resection of the bladder.	Weak
Perform prostate biopsy using the transperineal approach due to the lower risk of infectious complications.	Strong
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine in men prior to transrectal prostate biopsy.	Strong
Do not use fluoroquinolones for prostate biopsy in line with the European Commission final decision on EMEA/H/A-31/1452.	Strong
Use either target prophylaxis based on rectal swab or stool culture; augmented prophylaxis (two or more different classes of antibiotics); or alternative antibiotics (e.g. fosfomycin trometamol, cephalosporin, aminoglycoside) for antibiotic prophylaxis for transrectal biopsy.	Weak

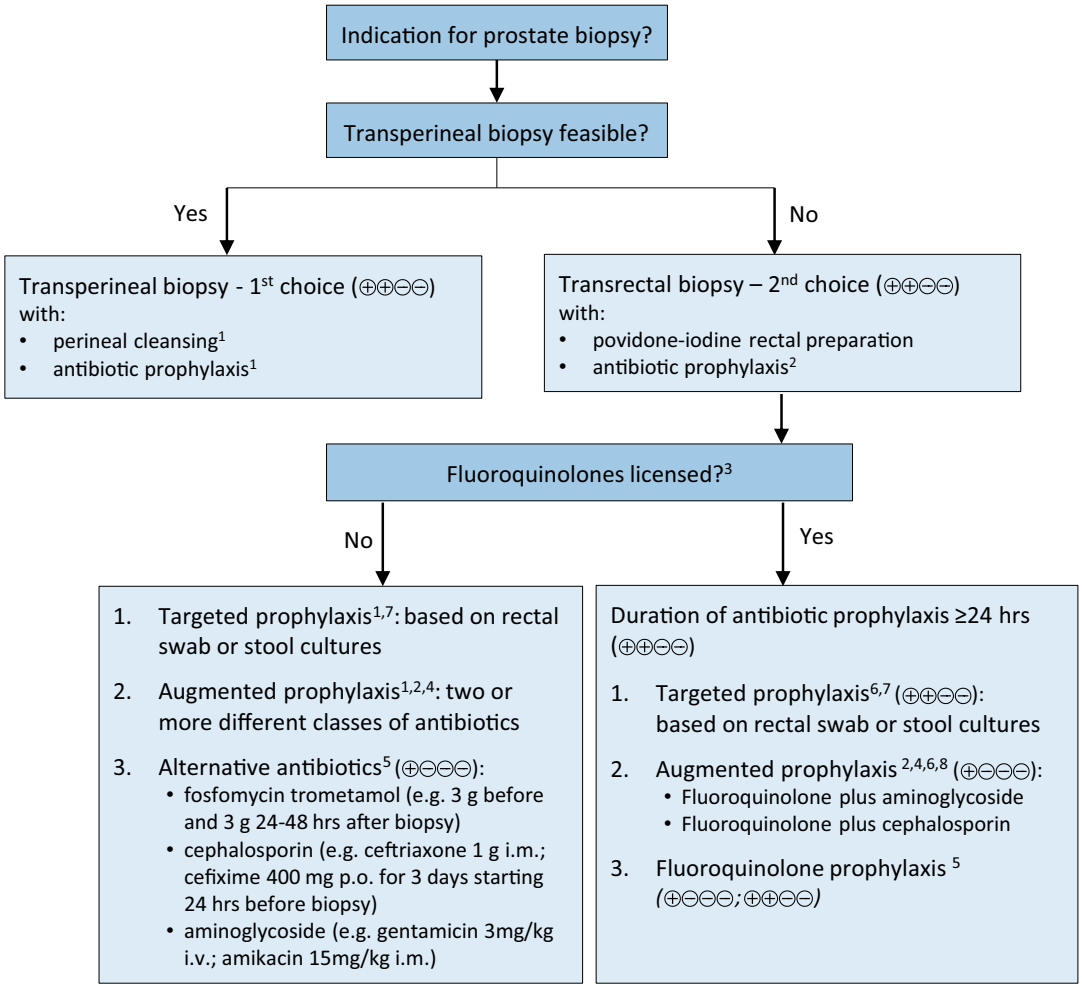
Table 12: Suggested regimens for antimicrobial prophylaxis prior to urological procedures.
As stated in section 3.15.1.4 the panel has decided not to make recommendations for specific agents for particular procedures, those listed below represent possible choices only. Urologists should choose a specific antimicrobial based on their knowledge of local pathogen prevalence for each type of procedure, their antibiotic susceptibility profiles and virulence.

Procedure	**Prophylaxis recommended**	**Antimicrobial**
Urodynamics	No	N/A
Cystoscopy	No	
Extracorporeal shockwave lithotripsy	No	

Ureteroscopy	Yes	Trimethoprim Trimethoprim-sulphamethoxazole Cephalosporin group 2 or 3 Aminopenicillin plus a beta-lactamase inhibitor
Percutaneous nephrolithotomy	Yes (single dose)	
Transurethral resection of the prostate	Yes	
Transurethral resection of the bladder	Yes, in patients who have a high risk of suffering post-operative sepsis.	
Transrectal prostate biopsy	Yes	1. Targeted prophylaxis - based on rectal swab or stool culture. 2. Augmented prophylaxis - two or more different classes of antibiotics*. 2. Alternative antibiotics • fosfomycin trometamol (e.g. 3 g before and 3 g 24-48 hrs after biopsy) • cephalosporin (e.g. ceftriaxone 1 g i.m.; cefixime 400 mg p.o. for 3 days starting 24 hrs before biopsy) • aminoglycoside (e.g. gentamicin 3mg/kg i.v.; amikacin 15mg/kg i.m.)

** Note option 2 is against antibiotic stewardship programmes.*
i.m. = intramuscular; i.v. intravenously; p.o. = orally.

Figure 4: Prostate biopsy workflow to reduce infectious complications


Indication for prostate biopsy?
Transperineal biopsy feasible?
Yes
No
Transperineal biopsy - 1st choice (⊕⊕⊖⊖) with:
• perineal cleansing[1]
• antibiotic prophylaxis[1]
Transrectal biopsy – 2nd choice (⊕⊕⊖⊖) with:
• povidone-iodine rectal preparation
• antibiotic prophylaxis[2]
Fluoroquinolones licensed?[3]
No
Yes
1. Targeted prophylaxis[1,7]: based on rectal swab or stool cultures
2. Augmented prophylaxis[1,2,4]: two or more different classes of antibiotics
3. Alternative antibiotics[5] (⊕⊖⊖⊖):
• fosfomycin trometamol (e.g. 3 g before and 3 g 24-48 hrs after biopsy)
• cephalosporin (e.g. ceftriaxone 1 g i.m.; cefixime 400 mg p.o. for 3 days starting 24 hrs before biopsy)
• aminoglycoside (e.g. gentamicin 3mg/kg i.v.; amikacin 15mg/kg i.m.)
Duration of antibiotic prophylaxis ≥24 hrs (⊕⊕⊖⊖)
1. Targeted prophylaxis[6,7] (⊕⊕⊖⊖): based on rectal swab or stool cultures
2. Augmented prophylaxis [2,4,6,8] (⊕⊖⊖⊖):
• Fluoroquinolone plus aminoglycoside
• Fluoroquinolone plus cephalosporin
3. Fluoroquinolone prophylaxis [5] (⊕⊖⊖⊖;⊕⊕⊖⊖)

1. No RCTs available, but reasonable intervention.
2. Be informed about local antimicrobial resistance.
3. Banned by European Commission due to side effects.

4. Contradicts principles of Antimicrobial Stewardship.
5. Fosfomycin trometamol (3 RCTs), cephalosporins (2 RCTs), aminoglycosides (2 RCTs).
6. Only one RCT comparing targeted and augmented prophylaxis.
7. Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.
8. Various schemes: fluoroquinolone plus aminoglycoside (3 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).
9. Significantly inferior to targeted and augmented prophylaxis.

Suggested workflow on how to reduce post biopsy infections. GRADE Working Group grades of evidence. High certainty: (⊕⊕⊕⊕) very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: (⊕⊕⊕⊖) moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: (⊕⊕⊖⊖) confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Figure reproduced from Pilatz et al., [479] with permission from Elsevier.
i.m. = intramuscular; i.v. intravenously; p.o. = orally.

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5. CONFLICT OF INTEREST

All members of the EAU Urological Infections Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publicly accessible through the EAU website: http://www.uroweb.org/guidelines/. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance, travel and meeting expenses. No honoraria or other reimbursements have been provided.

6. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

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EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

EAU Guidelines on

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1. INTRODUCTION

1.1 Aim and objectives

The European Association of Urology (EAU) Guidelines Panel for Urological Trauma have prepared these guidelines in order to assist medical professionals in the management of urological trauma in adults. Paediatric trauma is addressed in the EAU Paediatric Urology Guidelines [1].

It must be emphasised that clinical guidelines present the best evidence available to the experts but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions – also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urological Trauma Guidelines Panel consists of an international group of urologists and an interventional radiologist, all with particular expertise in urological trauma. All experts involved in the production of this document have submitted potential conflict of interest statements, which can be viewed on the EAU Website Uroweb: http://uroweb.org/guideline/urological-trauma/?type=panel.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. A number of translated versions, alongside several scientific publications in European Urology, the Associations scientific journal, are also available [2-5]. All documents can be viewed through the EAU website: http://uroweb.org/guideline/urological-trauma/.

1.4 Publication history

The Urological Trauma Guidelines were first published in 2003. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. All sections of the 2022 Urological Trauma Guidelines have been fully updated.

2. METHODS

2.1 Evidence sources

For the 2022 Urological Trauma Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Urological Trauma Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between April 1st 2020 and May 1st 2021. A total of 1,412 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://uroweb.org/guideline/urological-trauma/?type=appendices-publications. The majority of identified publications were comprised of case reports and retrospective case series. The lack of high-powered randomised controlled trials (RCTs) makes it difficult to draw meaningful conclusions. The panel recognises this critical limitation.

For each recommendation within the guidelines there is an accompanying online strength rating form the bases of which is a modified GRADE methodology [6, 7]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [8];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [9]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Peer review

The Urological trauma Guidelines was peer reviewed prior to publication in 2019.

3. EPIDEMIOLOGY, CLASSIFICATION & GENERAL MANAGEMNET PRINCIPALS

3.1 Definition and Epidemiology

Trauma is defined as a physical injury or a wound to living tissue caused by an extrinsic agent. Trauma is the sixth leading cause of death worldwide, accounting for 10% of all mortalities. It accounts for approximately five million deaths each year and causes disability to millions more [10, 11].

About half of all deaths due to trauma are in people aged 15-45 years; trauma is the leading cause of death in this age group [12]. Death from injury is twice as common in males, especially in relation to motor vehicle accidents (MVAs) and interpersonal violence. Trauma is therefore a serious public health problem with significant social and economic costs. Significant variation exists in the causes and the effects of traumatic injuries between geographical areas, and between low, middle, and high-income countries. It should be noted that alcohol and drug abuse increase the rate of traumatic injuries by precipitating interpersonal violence, child and sexual abuse, and MVAs.

3.2 Classification of trauma

Traumatic injuries are classified by the World Health Organization (WHO) into intentional (either interpersonal violence related, war-related or self-inflicted injuries), and unintentional injuries (mainly MVAs, falls, and other domestic accidents). Intentional trauma accounts for approximately half of the trauma-related deaths worldwide [11]. A specific type of unintentional injury is iatrogenic injury which occurs during therapeutic or diagnostic procedures by healthcare personnel. Traumatic insults are classified according to the basic mechanism of the injury into penetrating, when an object pierces the skin, and blunt injuries. Penetrating trauma is further classified according to the velocity of the projectile into:

1. high-velocity projectiles (e.g. rifle bullets - 800-1,000 m/sec);
2. medium-velocity projectiles (e.g. handgun bullets - 200-300 m/sec);
3. low-velocity items (e.g. knife stab).

High-velocity weapons inflict greater damage due to a temporary expansive cavitation that causes destruction in a much larger area than the projectile tract itself. In lower velocity injuries, the damage is usually confined to the projectile tract. Blast injury is a complex cause of trauma which includes blunt and penetrating trauma and burns.

The most commonly used classification grading system is the AAST (American Association for the Surgery of Trauma) injury scoring scale [13]. It is useful for managing renal trauma, but for the other urological organs, the injuries are commonly described by their anatomical site and severity (partial/complete).

3.3 General management principals

3.3.1 The Initial evaluation

The initial emergency assessment of a trauma patient is beyond the focus of these guidelines. It is usually carried out by emergency medicine and trauma specialised personnel following ATLS principles. Detailed further assessment involves cross-sectional imaging, laboratory analysis and specialist surgical input. The management of individual organ injury will follow in the sections below. Tetanus vaccine status should be assessed for all penetrating injuries.

3.3.2 ***Polytrauma managed in major trauma centres leads to improved survival***

Urological trauma is often associated with significant injuries in the polytraumatised patient [14]. Lessons from civilian trauma networks, military conflict, and mass casualty events have led to many advances in trauma care [15, 16]. These include the widespread acceptance of damage control principles and trauma centralisation to major trauma centres staffed by dedicated trauma teams. The re-organisation of care to these centres has been shown to reduce mortality by 25% and length of stay by four days [15]. Urologists increasingly understand their role in the context of polytrauma with the ultimate aims of improving survivability and decreasing morbidity in these patients.

3.3.3 ***Damage control***

Damage control is a life-saving strategy for severely injured patients that recognises the consequences of the lethal triad of trauma - hypothermia, coagulopathy and acidosis [17-19]. The first of a three phased approach consists of rapid control of haemorrhage and wound contamination. The second phase involves resuscitation in the intensive care unit (ICU), with the goal of restoring normal temperature, coagulation, and tissue oxygenation. The final stage involves definitive surgery when more time-consuming reconstructive procedures are performed in the stabilised patient [20]. Urological intervention needs to be mindful of the phase of management. Temporary abbreviated measures followed by later definitive surgery are required. Complex reconstructive procedures, including organ preservation, are not undertaken. The decision to enter damage control mode is taken by the lead trauma clinician following team discussion.

Urological examples include haemodynamically unstable patients due to suspected renal haemorrhage or pelvic fracture with associated urethral or bladder injury. The options of abdominal packing and temporary urinary drainage by ureteric, bladder or urethral catheterisation are valuable adjuncts to care.

3.3.4 ***Mass casualty events and Triage***

A mass casualty event is one in which the number of injured people and the severity of their injuries exceed the capability of the faculty and staff [21]. Triage, communication and preparedness are important components for a successful response.

Triage after mass casualty events involves difficult moral and ethical considerations. Disaster triage requires differentiation of the few critically injured individuals who can be saved by immediate intervention from the many others with non-life-threatening injuries for whom treatment can be delayed and from those whose injuries are so severe that survival is unlikely in the circumstances [22, 23].

3.3.5 ***The role of thromboprophylaxsis and bed rest***

Trauma patients are at high risk of deep venous thrombosis (DVT). Concerns with regard to secondary haemorrhage result in prolonged bed rest post-injury which effectively compounds this risk. Established prophylaxis measures reduce thrombosis and are recommended following systemic review [24]. However, the strength of evidence is not high and as yet there is no evidence to suggest that mortality or pulmonary embolism risk is reduced [25]. Compression stockings and low molecular weight heparins are favoured. The risk of secondary haemorrhage is thought to be low and the practice of strict bed rest has waned in patients who are able to mobilise.

3.3.6 ***Antibiotic stewardship***

Single shot antibiotic doses are common in major trauma. The indication for continuing antibiotics is governed by injury grade, associated injuries and the need for intervention. Patients with urinary extravasation tend to be kept on antibiotics but there is no evidence base for this. Antibiotics should be avoided in lesser trauma e.g. Grade 1-3 renal trauma, and regular review undertaken for those continued on regular dosing.

3.3.7 ***Urinary catheterisation***

Prolonged catheterisation is required in all forms of bladder and urethral injury. Catheterisation is not necessary in stable patients with low-grade renal injury. Patients with heavy haematuria, who require monitoring or ureteric stenting, benefit from catheterisation. This can be removed once haematuria lightens and there is an improvement in the clinical situation. The shortest possible period of catheterisation is advised.

4. UROGENITAL TRAUMA GUIDELINES

4.1 Renal Trauma

4.1.1 Epidemiology, aetiology and pathophysiology

Renal trauma is present in up to 5% of all trauma cases [26]. It is most common in young males and has an overall population incidence of 4.9 per 100,000 [27]. Most injuries can be managed non-operatively with successful organ preservation [28-31].

Blunt injuries result from MVAs, falls, sporting injuries, and assault [32]. The kidney and/or hilar structures are directly crushed as a result. Less commonly, sudden deceleration may result in an avulsion injury affecting the vascular structures of the hilum or the ureteropelvic junction (UPJ).

Penetrating injuries are due to stab and gunshot wounds. They tend to be more severe and less predictable than blunt trauma. The prevalence is higher in urban settings [33]. Penetrating injury produces direct tissue disruption of the parenchyma, vascular pedicles, or collecting system. High-velocity bullets or fragments have the potential for greatest parenchymal destruction and are most often associated with multiple-organ injuries [34].

The most commonly used classification system is that of the AAST [13]. It is validated and predicts morbidity and the need for intervention [35, 36]. This remains the most useful of urological trauma classifications; however, the majority of Grade 1 - 4 injuries are now managed conservatively and debate has centred around updating the classification of high-grade injury i.e. identifying the injuries most likely to benefit from early angiographic embolisation, repair or nephrectomy [29, 37].

Table 4.1.1: AAST renal injury grading scale adapted from Kozar *et al.*, [13]

Grade*	Type of injury	Description of injury
1	Haematoma and/or Contusion	Subcapsular non-expanding haematoma or parenchymal contusion without parenchymal laceration.
2	Haematoma	Non-expanding perirenal haematoma confirmed to Gerta fascia.
	Laceration	Renal parenchymal laceration ≤ 1 cm depth without urinary extravasation.
3	Laceration	Renal parenchymal laceration ≤ 1 cm depth without collecting system rupture or urinary extravasation.
4	Laceration	Parenchymal laceration extending into urinary collecting system with urinary extravasation. Renal pelvis laceration and/or complete ureteropelvic disruption.
	Vascular	Segmental renal vein or artery injury. Segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding.
5	Laceration	Shattered kidney with loss of identifiable parenchymal renal anatomy.
	Vascular	Main renal artery or vein laceration or avulsion of renal hilum. Devascularized kidney with active bleeding.

**Advance one grade for bilateral injuries up to Grade 3.*

Note: The AAST renal injury scale was updated in 2018 and is presented in Table 4.1.1; however, all references included in this text are based on the AAST 1989 renal injury scale. The 2018 injury scale does not outperform the previous grading system in predicting bleeding and the need for treatment intervention and does not impact on the validity of the current recommendations [38].

4.1.2 Evaluation

The evaluation of stable patients with renal trauma is now based on a trauma protocol computed tomography (CT) scan, often performed prior to involvement of a urologist [39, 40]. It is important to consider all parameters in the evaluation of the patient and to understand the indications for scanning when these are not absolute. Indicators of injury include a direct blow to the flank or rapid deceleration event (fall, high-speed MVAs). Special consideration should be given to pre-existing renal disease [41] or the injured solitary kidney [42]. Pre-existing abnormality e.g. hydronephrosis makes injury more likely following trauma [43].

Vital signs should be recorded throughout the initial evaluation and give the most reliable indication of the urgency of the situation. Physical examination may reveal flank bruising, stab wounds, or bullet entry or exit wounds and abdominal tenderness.

Urinalysis, haematocrit and baseline creatinine are required. Haematuria (visible or non-visible) is the key finding. However, major injury such as disruption of the UPJ, pedicle injuries, segmental arterial thrombosis and stab wounds may not have haematuria [44-46]. Haematuria that is out of proportion to the history of

trauma may suggest pre-existing pathology [47]. Urine dipstick quickly evaluates for haematuria, but false-negative results can range from 3-10% [48]. An increased creatinine level usually reflects pre-existing renal pathology.

*4.1.3 **Imaging: criteria for radiographic assessment***

The goals of imaging are to grade the renal injury, document pre-existing renal pathology, demonstrate presence of the contralateral kidney and identify injuries to other organs. Haemodynamic status will determine the initial imaging pathway with unstable patients potentially requiring immediate intervention. The majority of patients with moderate to major trauma will have had a CT scan performed soon after presentation. In patients who have not had any imaging the indications for renal imaging are [32, 49-52]:

- visible haematuria;
- non-visible haematuria and one episode of hypotension;
- a history of rapid deceleration injury and/or significant associated injuries;
- penetrating trauma;
- clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.

4.1.3.1 Computed tomography

Computed tomography is the imaging modality of choice in stable patients. It is quick, widely available, and can accurately identify grade of renal injury [53], establish the presence of the contralateral kidney and demonstrate concurrent injuries to other organs. It is ideally performed as a three-phase study [54]:

1. The arterial phase assesses vascular injury and presence of active extravasation of contrast.
2. The nephrographic phase optimally demonstrates parenchymal contusions and lacerations.
3. The delayed phase imaging (5 minutes) identifies collecting system/ureteric injury.

In practice, trauma patients usually undergo standardised whole-body imaging protocols and delayed phase imaging of the renal tract is not routinely performed. If there is suspicion that renal injuries have not been fully evaluated, delayed phase imaging is recommended. The rates of contrast-induced nephropathy seen in trauma patients is low [55].

4.1.3.2 Ultrasonography (US)

In the primary survey of a critically injured patient, FAST (Focused Assessment Sonography in Trauma) is used to identify haemoperitoneum as cause of haemorrhage and hypovolemia. However, it is not routinely used for the assessment of solid organ injury as it is insensitive, operator dependant, does not define the injury well, and is inferior to CT. It is an option for follow-up [56-58].

4.1.3.3 Intravenous pyelography (IVP)

Intravenous pyelography has been superseded by cross-sectional imaging and should only be performed when CT is not available [50]. One-shot intra-operative IVP can be used to confirm the presence of a functioning contralateral kidney in patients too unstable to have had pre-operative imaging [59]. The technique consists of a bolus intravenous injection of 2 mL/kg of radiographic contrast followed by a single plain film taken after ten minutes. The quality of the resulting imaging is generally poor. Palpation of the contralateral (unaffected) kidney is a pragmatic surrogate of function [18].

4.1.3.4 Magnetic resonance imaging (MRI)

The diagnostic accuracy of MRI in renal trauma is similar to that of CT [60, 61]. However, the logistical challenges of MRI make this modality impractical in acute trauma.

4.1.3.5 Radionuclide scans

Radionuclide scans do not play a role in the immediate evaluation of renal trauma patients. In the longer term, follow-up scans can be used to identify areas of scarring, functional loss or obstruction [62].

*4.1.4 **Disease management***

4.1.4.1 Non-operative management

The non-operative management of renal trauma can be viewed as a “package of care”; a step-wise approach starting with conservative treatment, followed by minimally invasive and/or surgical exploration, if necessary. It should be noted that an algorithm for “package of care” will vary in different centres according to available interventions; however, the importance of escalation in treatment interventions should be emphasised [29]. This approach has likely resulted in the rate of nephrectomy for high-grade renal injuries decreasing over time [63].

4.1.4.1.1 Blunt renal injuries

Haemodynamic stability is the primary criterion for the management of all renal injuries. Non-operative management has become the treatment of choice for most cases. In stable patients, this means a period of bed rest, serial blood tests, regular observation and re-imaging as indicated. Primary conservative management is associated with a lower rate of nephrectomies, and no increase in immediate or long-term morbidity [64].

Grade 1 - 3 injuries are managed non-operatively [65, 66]. Grade 4 injuries are also mostly treated conservatively, but the requirement for subsequent intervention is higher [67]. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement and/or percutaneous drainage [68].

Grade 5 injuries often present with haemodynamic instability and major associated injuries. There is thus a higher rate of exploration and nephrectomy [69, 70]. However, several studies now support expectant management in patients with Grade 4 and 5 injuries [29, 30, 71-75]. Similarly, unilateral main arterial injuries or arterial thrombosis are normally managed non-operatively in haemodynamically stable patients with surgical repair reserved for bilateral artery injuries or injuries involving a solitary functional kidney [76]. Pre-hospital prolonged warm ischaemia usually results in irreparable damage and renal loss.

One study designed a normogram to predict the need for an intervention to stop bleeding in high-grade renal trauma. Factors which increased risk of intervention were a haematoma size of > 12 cm, penetrating trauma, vascular contrast extravasation, pararenal haematoma extension, concomitant injuries and shock [77].

4.1.4.1.2 Penetrating renal injuries

Penetrating abdominal wounds have traditionally been managed surgically. However, selective non-operative management of penetrating abdominal wounds is now accepted following detailed assessment in stable patients [67, 78-80].

For renal injuries, the site of the wound, haemodynamic stability, and diagnostic imaging are the main determinants for intervention. The majority of low-grade stab wounds posterior to the anterior axillary line can be managed non-operatively in stable patients [81]. Grade 3 or higher injuries due to stab wounds in stable patients can be managed expectantly, but warrant closer observation as the clinical course is more unpredictable and associated with a higher rate of delayed intervention [81, 82]. High-grade injuries, concomitant abdominal injuries and gunshot wounds are most likely to fail non-operative management [80]. Overall, non-operative management of penetrating injuries in selected stable patients is associated with a successful outcome in up to 50% of stab wounds and up to 40% of gunshot wounds [30, 83-86].

4.1.4.1.3 Selective angioembolisation

Selective angioembolisation (AE) has a key role in the non-operative management of blunt renal trauma in haemodynamically stable patients [87-89]. Currently there are no validated criteria to identify patients who require AE and its use in renal trauma remains heterogeneous. Accepted CT findings indicating the need for AE are active extravasation of contrast, arteriovenous fistula (AVF) and pseudo-aneurysm [90]. The presence of both active extravasation of contrast and a large haematoma (> 25 mm depth) predict the need for AE with good accuracy [90, 91].

Angioembolisation has been utilised in the non-operative management of all grades of renal injury; however, it is likely to be most beneficial in the setting of high-grade renal trauma (AAST > 3) [87-89]. Non-operative management of high-grade renal trauma, where AE is included in the management algorithm, can be successful in up to 94.9% of Grade 3, 89% of Grade 4 and 52% of Grade 5 injuries [87, 88]. Increasing grade of renal injury is associated with increased risk of failed AE and need for repeat intervention [92]. Gross haematuria, haemodynamic instability, Grade 5 trauma and urinary extravasation are significant predictors of selective AE failure [93].

Repeat embolisation prevents nephrectomy in 67% of patients. Open surgery after failed embolisation usually results in nephrectomy [92, 94]. Despite concerns regarding parenchymal infarction and the use of iodinated contrast media, AE does not appear to affect the occurrence or course of acute kidney injury following renal trauma [95]. For high-grade injuries, AE has also been shown to have a high success rate and to provide the greatest protection of renal function, with no difference in renal function after long-term follow-up [96]. In severe polytrauma or high operative risk, the main artery may be embolised, either as a definitive treatment or as a step to a more controlled nephrectomy.

The evidence supporting AE in penetrating renal trauma is sparse. One study found that AE is three times more likely to fail in penetrating trauma [78]. However, AE has been used successfully to treat acute haemorrhage, AVF and pseudo-aneurysms resulting from penetrating renal trauma [97].

4.1.4.1.4 Urinary catheterisation

Catheterisation is not necessary in stable patients with low-grade injury. Patients with severe visible haematuria, who require monitoring or stenting, benefit from catheterisation. A longer period of catheterisation is required if a stent is placed. Once the haematuria lightens and the patient is mobile, the catheter should be removed.

4.1.4.1.5 Repeat imaging (early)

Computed tomography scans should be performed on patients with fever, unexplained decreased haematocrit or significant flank pain. Repeat imaging is also recommended in high-grade injury and in penetrating trauma two to four days after trauma to minimise the risk of missed complications. Repeat imaging can be safely omitted for patients with Grade 1-3 injuries as long as they remain clinically well [98].

4.1.4.2 Surgical management

4.1.4.2.1 Indications for renal exploration

A non- or transient-response to initial fluid resuscitation is an strong indication for exploration [78, 79]. There is a trend towards ongoing resuscitation and AE [99]. Exploration is influenced by aetiology and grade of injury, transfusion requirements, the need to explore associated abdominal injuries, and the discovery of an expanding or pulsatile peri-renal haematoma at laparotomy [100]. Grade 5 vascular injury is an absolute indication for exploration [35].

4.1.4.2.2 Operative findings and reconstruction

The overall exploration rate for blunt trauma is low [101]. The goals of exploration following renal trauma are control of haemorrhage and renal salvage. Most series recommend the transperitoneal approach for surgery [102, 103]. Entering the retroperitoneum and leaving the confined haematoma undisturbed within the perinephric fascia is recommended; temporarily packing the fossa tightly with laparotomy pads can salvage the kidney in instances of intra-operative haemorrhage [104]. Access to the pedicle is obtained either through the posterior parietal peritoneum, which is incised over the aorta, just medial to the inferior mesenteric vein or by bluntly dissecting along the plane of the psoas muscle fascia, adjacent to the great vessels, and directly placing a vascular clamp on the hilum [104].

Stable haematomas detected during exploration for associated injuries should not be opened. Central or expanding haematomas indicate injuries of the renal pedicle, aorta, or vena cava and are potentially life-threatening and warrant further exploration [105].

Feasibility of renal reconstruction should be judged during the operation. The overall rate of patients who undergo a nephrectomy during exploration is approximately 30% [106]. Other intra-abdominal injuries also increase the likelihood of nephrectomy [107]. Mortality is associated with overall severity of the injury and not often a consequence of the renal injury itself [108]. High velocity gunshot injuries make reconstruction difficult and nephrectomy is usually required [109]. Since nephrectomy is independently associated with increased risk of mortality in injured patients it should be avoided when possible [110].

Renorrhaphy is the most common reconstructive technique. Partial nephrectomy is required when non-viable tissue is detected. Watertight closure of the collecting system is desirable, although closing the parenchyma over the injured collecting system is acceptable.

The use of haemostatic agents and sealants in reconstruction is helpful [111]. In all cases, drainage of the ipsilateral retroperitoneum is recommended.

The repair of vascular injuries is seldom, if ever, effective [112]. Repair should be attempted in patients with a solitary kidney or bilateral injuries [113]. Nephrectomy for main artery injury has outcomes similar to those of vascular repair and does not worsen post-treatment renal function in the short-term. Bleeding or dissection of the main renal artery may also be managed with a stent.

4.1.5 ***Follow-up***

The risk of complications relates to aetiology, injury grade, and mode of management [114, 115]. Follow-up includes physical examination, urinalysis, diagnostic imaging, blood pressure measurement and serum creatinine [69]. Potential complications are primarily identified by imaging; however, follow-up imaging is not recommended in low-grade uncomplicated injury. Ultrasound can be used to define the post-injury anatomy avoiding further ionising radiation. Nuclear scans are useful for documenting functional recovery following renal injury and reconstruction [62]. Annual blood pressure monitoring is recommended to exclude renovascular hypertension [116].

4.1.5.1 Complications

Early (≤ 1 month) complications include bleeding, infection, perinephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation and urinoma. Delayed complications include bleeding, hydronephrosis, calculus formation, chronic pyelonephritis, hypertension, AVF, hydronephrosis and pseudo-aneurysms. Bleeding may be life-threatening with elective angiographic embolisation the preferred treatment [117]. Perinephric abscess formation is initially managed by percutaneous drainage [101].

Hypertension is rare [118, 119]. It may occur acutely as a result of external compression from peri-renal haematoma (Page kidney), chronically due to compressive scar formation, or as a result of renal artery thrombosis, segmental arterial thrombosis, renal artery stenosis (Goldblatt kidney), or AVF. Arteriography may be required. Treatment, including medical management, excision of the ischaemic parenchymal segment, vascular reconstruction, or nephrectomy, is indicated if hypertension persists [116].

Arteriovenous fistulae usually present with delayed onset of significant haematuria, most often after penetrating trauma. Percutaneous embolisation is often effective for symptomatic AVF, but larger fistulae may require surgery [120]. The development of pseudo-aneurysm is a rare complication following blunt trauma.

*4.1.6 **Iatrogenic renal injuries***

Iatrogenic renal trauma needs to be recognised and managed promptly to minimise morbidity and mortality. The most common causes of iatrogenic renal injuries are percutaneous access to kidney, stone surgery, cancer surgery (laparoscopic and open) and transplantation [3]. The diagnosis and management follow the same principles as outlined previously.

*4.1.7 **Summary of evidence and recommendations for evaluation and management of renal trauma***

Summary of evidence	**LE**
Vital signs on admission give the most reliable indication of the urgency of the situation.	3
Special consideration should be given to patients with a solitary kidney and pre-existing renal disease.	4
Haematuria is a key finding following renal trauma; although, it may not be present in certain situations.	3
A multiphase CT scan is the best method for the diagnosis and staging of renal injuries in haemodynamically stable patients.	3
Haemodynamic stability is the primary criterion for selecting patients for non-operative management.	3
Selective angioembolisation is effective in patients with active bleeding from renal injury, without other indications for immediate abdominal operation.	3
Renal reconstruction should be attempted if haemorrhage is controlled and there is sufficient viable renal parenchyma.	3
Iatrogenic renal injuries are procedure-dependent (1.8-15%); the most common injuries are vascular.	3
Limited literature exists with regard to long-term consequences of renal trauma. Current follow-up includes physical examination, urinalysis, diagnostic imaging, serum creatinine, as well as annual blood pressure monitoring to diagnose renovascular hypertension.	4

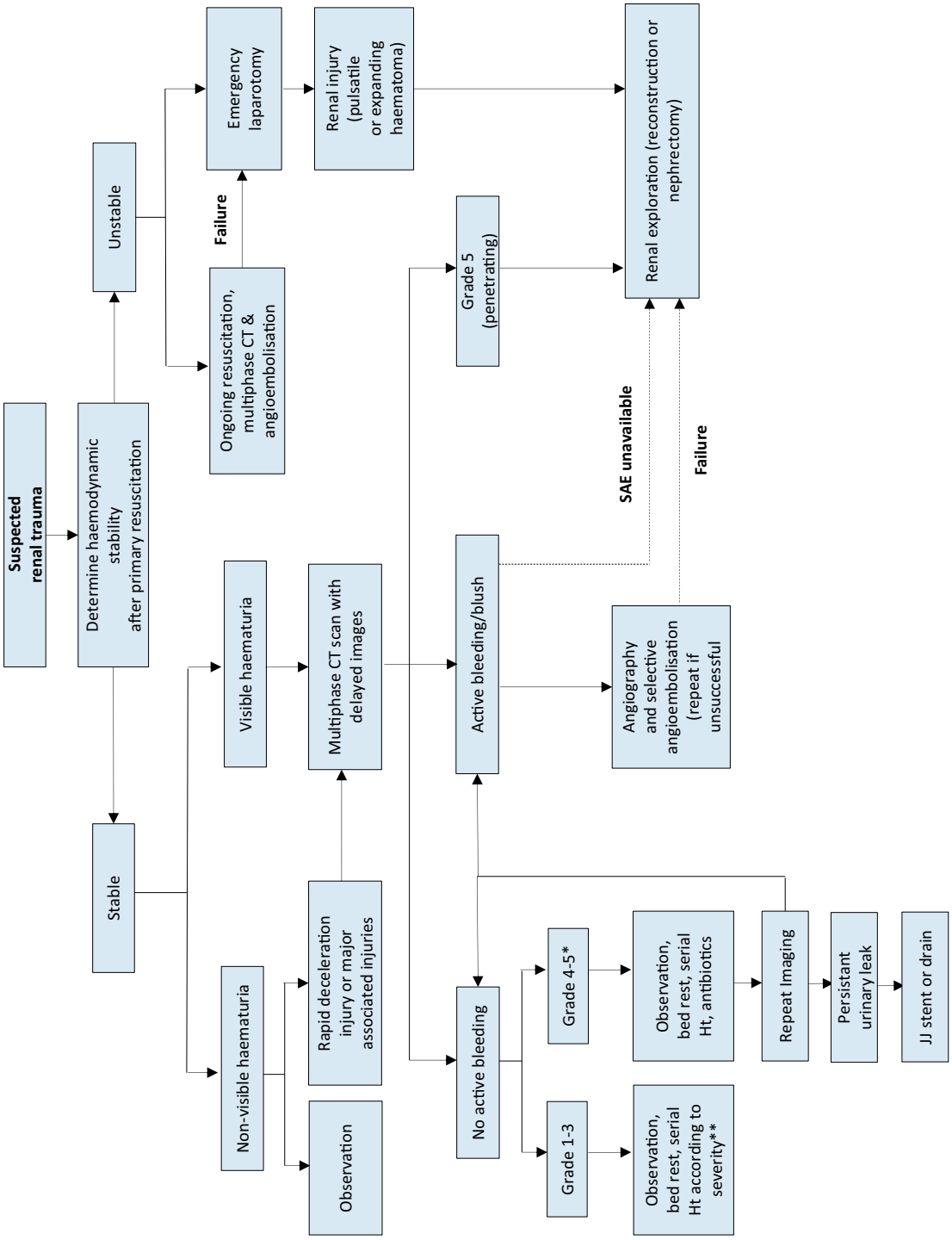
Recommendations	**Strength rating**
Evaluation	
Assess haemodynamic stability upon admission.	Strong
Record past renal surgery, and known pre-existing renal abnormalities (ureteropelvic junction obstruction, solitary kidney, lithiasis).	Strong
Test for haematuria in a patient with suspected renal injury.	Strong
Perform a multiphase computed tomography scan in trauma patients with: • visible haematuria; • non-visible haematuria and one episode of hypotension; • a history of rapid deceleration injury and/or significant associated injuries; • penetrating trauma; • clinical signs suggesting renal trauma e.g. flank pain, abrasions, fractured ribs, abdominal distension and/or a mass and tenderness.	Strong
Management	
Manage stable patients with blunt renal trauma non-operatively with close monitoring and re-imaging as required.	Strong
Manage isolated Grade 1-4 stab and low-velocity gunshot wounds in stable patients non-operatively.	Strong

Use selective angioembolisation for active renal bleeding if there are no other indications for immediate surgical exploration.	Strong
Proceed with renal exploration in the presence of: • persistent haemodynamic instability; • Grade 5 vascular or penetrating injury; • expanding or pulsatile peri-renal haematoma.	Strong
Attempt renal reconstruction if haemorrhage is controlled and there is sufficient viable renal parenchyma.	Weak
Repeat imaging in high-grade and penetrating injuries and in cases of fever, worsening flank pain, or falling haematocrit.	Strong
Follow-up approximately three months after major renal injury with: • physical examination; • urinalysis; • individualised radiological investigation including nuclear scintigraphy; • blood pressure measurement; • renal function tests.	Weak
Measure blood pressure annually to diagnose renovascular hypertension.	Strong

4.1.8 ***Treatment algorithms***

Management of renal trauma

Figure 4.1.1 Management of renal trauma



** Excluding Grade 5 penetrating injuries.*

*** Antibiotics should be administered for all penetrating injuries.*

--- If haemodynamically unstable.

CT = computed tomography; Ht = haematocrit; SAE = selective angioembolisation.

4.2 Ureteral Trauma

*4.2.1 **Incidence***

Trauma to the ureters is relatively rare as they are protected from injury by their small size, mobility, and the adjacent vertebrae, bony pelvis and muscles. Iatrogenic trauma is the most common cause of ureteral injury (approximately 80%) [121]. It is seen in open, laparoscopic or endoscopic surgery and is often missed intra-operatively. Any trauma to the ureter may result in severe sequelae [122].

*4.2.2 **Epidemiology, aetiology, and pathophysiology***

Overall, ureteral trauma accounts for 1-2.5% of urinary tract trauma [121, 123-125], with even higher rates in modern combat injuries [126]. Penetrating external ureteral trauma, mainly caused by gunshot wounds, dominates most of the modern series, both civilian and military [121, 123, 127]. About one-third of cases of external trauma to the ureters are caused by blunt trauma, mostly MVAs [124, 125].

Ureteral injury should be suspected in all cases of penetrating abdominal injury, especially gunshot wounds, as it occurs in 2-3% of cases [121]. It should also be suspected in blunt trauma with a deceleration mechanism, as the renal pelvis can be torn away from the ureter [121]. The distribution of external ureteral injuries along the ureter varies between series, but it is more common in the upper ureter [123-125].

Iatrogenic ureteral trauma can result from various mechanisms: ligation or kinking with a suture, crushing from a clamp, partial or complete transection, thermal injury, or ischaemia from devascularisation [127-129]. It usually involves the lower ureter [121, 127, 128, 130]. Gynaecological operations are the most common cause of iatrogenic trauma (Table 4.2.1), but it may also occur in colorectal operations, especially abdominoperineal resection and low anterior resection [131, 132]. The incidence of urological iatrogenic trauma has decreased in the last twenty years due to improvements in technique, instruments and surgical experience [127, 133]. In colorectal surgery there has been a significant decrease in the rate of ureteral injury for robot-assisted procedures [134]. However, minimally invasive laparoscopic/robotic hysterectomy techniques have not further reduced the rate of ureteral injuries [135-137].

Ureteroscopy is a common cause of iatrogenic ureteric trauma up to 71.6% in some series [138]. The post-ureteroscopic lesion scale (PULS) may standardise intra-operative traumatic findings during ureteroscopy [139]. A smaller proximal ureter diameter in non-contrast CT is a predictor for high-grade ureteral injury during ureteral access sheath (UAS) placement [140]. In a small RCT pre-operative Silodosin 8 mg for three days significantly reduced Grade 2 or higher ureteral injuries, due to UAS insertion [141]. Male gender, longer operation and UAS insertion times are predictors for high grade ureteric injury [138].

Risk factors for iatrogenic trauma include conditions that alter the normal anatomy, e.g. advanced malignancy, prior surgery or irradiation, diverticulitis, endometriosis, anatomical abnormalities, and major haemorrhage [127, 131, 142, 143]. Occult ureteral injury occurs more often than reported and not all injuries are diagnosed intra-operatively [122].

Table 4.2.1: Incidence of ureteral injury in various procedures

Procedure	Percentage %
Gynaecological [130, 144-146]	
Emergency caesarean delivery	0.01 – 0.06
Vaginal hysterectomy	0.02 – 0.5
Abdominal hysterectomy	0.03 – 2.0
Laparoscopic hysterectomy	0.13 – 6.0
Urogynaecological (anti-incontinence/prolapse)	1.7 – 4.3
Colorectal [129, 134, 144, 147, 148]	0.15 – 10
Ureteroscopy [133]	
Mucosal abrasion	0.3 – 4.1
Ureteral perforation	0.2 – 2.0
Intussusception/avulsion	0 – 0.3
Post-chemotherapy lymph node dissection for non-seminoma germ cell tumours	0.02
Radical prostatectomy [150]	
Open retropubic	0.05 – 1.6
Robot-assisted	0.05 – 0.4

4.2.3 ***Diagnosis***

The diagnosis of ureteral trauma is challenging; therefore, a high index of suspicion should be maintained. In penetrating external trauma, it is usually made intra-operatively during laparotomy [151], while it is delayed in most blunt trauma and iatrogenic cases [127, 130, 152].

4.2.3.1 Clinical diagnosis

External ureteral trauma usually accompanies severe abdominal and pelvic injuries. Penetrating trauma is usually associated with vascular and intestinal injuries, while blunt trauma is associated with damage to the pelvic bones and lumbosacral spinal injuries [124, 125]. Haematuria is an unreliable and poor indicator of ureteral injury, as it is present in only 50-75% of patients [121, 127, 153].

Iatrogenic injury may be noticed during the primary procedure, when intravenous dye (e.g. indigo carmine) is injected to exclude ureteral injury. Early recognition facilitates immediate repair and provides better outcome [142, 151]. However, it is usually noticed later in the same admission, when it is discovered by subsequent evidence of upper tract obstruction, urinary fistulae formation or sepsis. The following clinical signs are characteristic of delayed diagnosis flank pain, urinary incontinence, vaginal or drain urinary leakage, haematuria, fever and uraemia or urinoma. When the diagnosis is missed, the complication rate increases [121, 126, 152].

4.2.3.2 Radiological diagnosis

Multi-phase CT is the mainstay imaging technique for trauma patients. Generally, it is widely available and allows for multi-phasic assessment of all of the structures in the pelvis and abdomen. Computed tomography urography (CTU) is the examination of choice when ureteral injuries are suspected [154]. Extravasation of contrast medium in the delayed phase is the hallmark sign of ureteral trauma. However, hydronephrosis, ascites, urinoma or mild ureteral dilation are often the only signs. In unclear cases, a retrograde or antegrade urography is the optimum standard for confirmation [127]. Intravenous pyelography, especially one-shot IVP, is unreliable in diagnosis, as it is negative in up to 60% of patients [121, 127].

4.2.4 ***Prevention of iatrogenic trauma***

The prevention of iatrogenic trauma to the ureters depends upon the visual identification of the ureters and careful intra-operative dissection in their proximity [127-129]. The use of prophylactic pre-operative ureteral stent insertion assists in visualisation and palpation and is used in complicated cases (about 4% in a large cohort) [155, 156] or patients with previous surgery [157]. It is probably also advantageous in making it easier to detect ureteral injury intra-operatively [128]; however, it is not associated with a decrease in the likelihood of ureteric injury [148]. Apart from its evident disadvantages (potential complications, increased surgical time and cost), a stent may alter the location of the ureter and diminish its flexibility [128, 147]. A retrograde instillation of indocyanine green in the ureters has been shown to safely allow their identification and preservation in complex robotic-assisted colorectal surgeries [158, 159].

4.2.5 ***Management***

Management of ureteral trauma depends on many factors concerning the nature, severity and location of the injury. Immediate diagnosis of a ligation injury during an operation can be managed by de-ligation and stent placement. Partial injuries can be repaired immediately with a stent or urinary diversion via a nephrostomy tube. Stenting is helpful because it provides canalisation and may decrease the risk of stricture [127, 160]. On the other hand, its insertion has to be weighed against potentially aggravating the severity of the ureteral injury. Immediate repair of complete ureteral injury is usually advisable as it significantly decreases the need for secondary or tertiary procedures compared to delayed repair [160]. The ureter is mobilised on both ends and a spatulated end-to-end anastomosis is performed. Primary repair by uretero-ureterostomy or ureteric re-implantation can be safely performed laparoscopically at the time of the iatrogenic injury, with good mid-term results [161]. In cases of unstable trauma patients, a ‘damage control’ approach is preferred with ligation of the ureter, diversion of the urine (e.g. via a nephrostomy), and a delayed definitive repair [162]. A national trauma database study reported that the majority of blunt low- and high-severity traumatic ureteric injuries in both stable and unstable patients were treated by nephrostomy or stenting [163]. Ureteral reconstruction was more frequently performed in high-grade injuries in unstable patients. Exploratory laparotomy for associated traumatic injuries was a predictor for immediate ureteral reconstruction [163]. Injuries that are diagnosed late are usually managed first by placement of a nephrostomy tube or stent [127].

Endo-urological treatment of delayed-diagnosed ureteral injuries by internal stenting, with or without dilatation, is the first step in most cases. It is performed either retrogradely or antegradely through a percutaneous nephrostomy, and it has a variable success rate of 14-19% [164-166]. An open or robot-assisted laparoscopic surgical repair is necessary in case of failure [167]. The basic principles for any surgical repair of a ureteral injury are outlined in Table 4.2.2. Wide debridement is highly recommended for gunshot wound injuries due to the ‘blast effect’ of the injury.

4.2.5.1 Proximal and mid-ureteral injury

Injuries shorter than 2-3 cm can usually be managed by a primary uretero-ureterostomy [121]. When this approach is not feasible, a uretero-calycostomy should be considered. In case of a large extra-renal pelvis and a stricture at the UPJ, a pelvic spiral flap according to Culp-DeWeerd is an option [168]. In extensive ureteral loss, a transuretero-ureterostomy is a valid option, where the proximal stump of the ureter is transposed across the midline and anastomosed to the contralateral ureter. The reported stenosis rate is 4% and re-intervention or revision occur in 10% of cases [169].

4.2.5.2 Distal ureteral injury

Distal injuries are best managed by ureteral re-implantation (uretero-neocystostomy) because the primary trauma usually jeopardises the blood supply to the distal ureter. The question of refluxing vs. non-refluxing ureteral re-implantation remains unresolved in the literature. The risk for clinically significant reflux should be weighed against the risk for ureteral obstruction.

A psoas hitch between the bladder and the ipsilateral psoas tendon is usually needed to bridge the gap and to protect the anastomosis from tension. The contralateral superior vesical pedicle may be divided to improve bladder mobility. The reported success rate is very high (97%) [169]. In extensive mid-lower ureteral injury, the large gap can be bridged with a tubularised L-shaped bladder flap (Boari flap). It is a time-consuming operation and not usually suitable in the acute setting. The success rate is reported to be 81-88% [170].

4.2.5.3 Long segment ureteral injury

A longer ureteral injury can be replaced using a segment of the intestines, usually the ileum (ileal interposition graft). This should be avoided in patients with impaired renal function or known intestinal disease. Follow-up should include serum chemistry to diagnose hyperchloremic metabolic acidosis [171]. The long-term complications include anastomotic stricture (3%) and fistulae (6%) [172]. Another option could be downward nephropexy associated with a long Boari flap. In cases of extensive ureteral loss or after multiple attempts at ureteral repair, the kidney can be relocated to the pelvis (auto-transplantation). The renal vessels are anastomosed to the iliac vessels and a ureteral re-implantation is performed [173, 174].

Buccal mucosa ureteroplasty is another option for long segment ureteral injury, especially after a previous failed reconstruction, as an alternative to auto-transplantation. The overall success rate is 90%, but experience is limited [175].

4.2.5.4 Permanent urinary diversion/nephrectomy

Following early or late repairs, up to 38% patients develop secondary ureteric strictures requiring interventions [176] or palliative management by indwelling ureteric catheter or nephrostomy tube [160, 177]. Moreover, in some series up to 10% of failed repairs have evidence of renal parenchyma or function loss, leading to nephrectomy [160, 176].

Table 4.2.2: Principles of surgical repair of ureteral injury

Debridement of necrotic tissue
Spatulation of ureteral ends
Watertight tension-free mucosa-to-mucosa anastomosis using absorbable sutures
Internal stenting
External drain
Isolation of injury with peritoneum or omentum

4.2.6 Summary of evidence and recommendations for the management of ureteral trauma

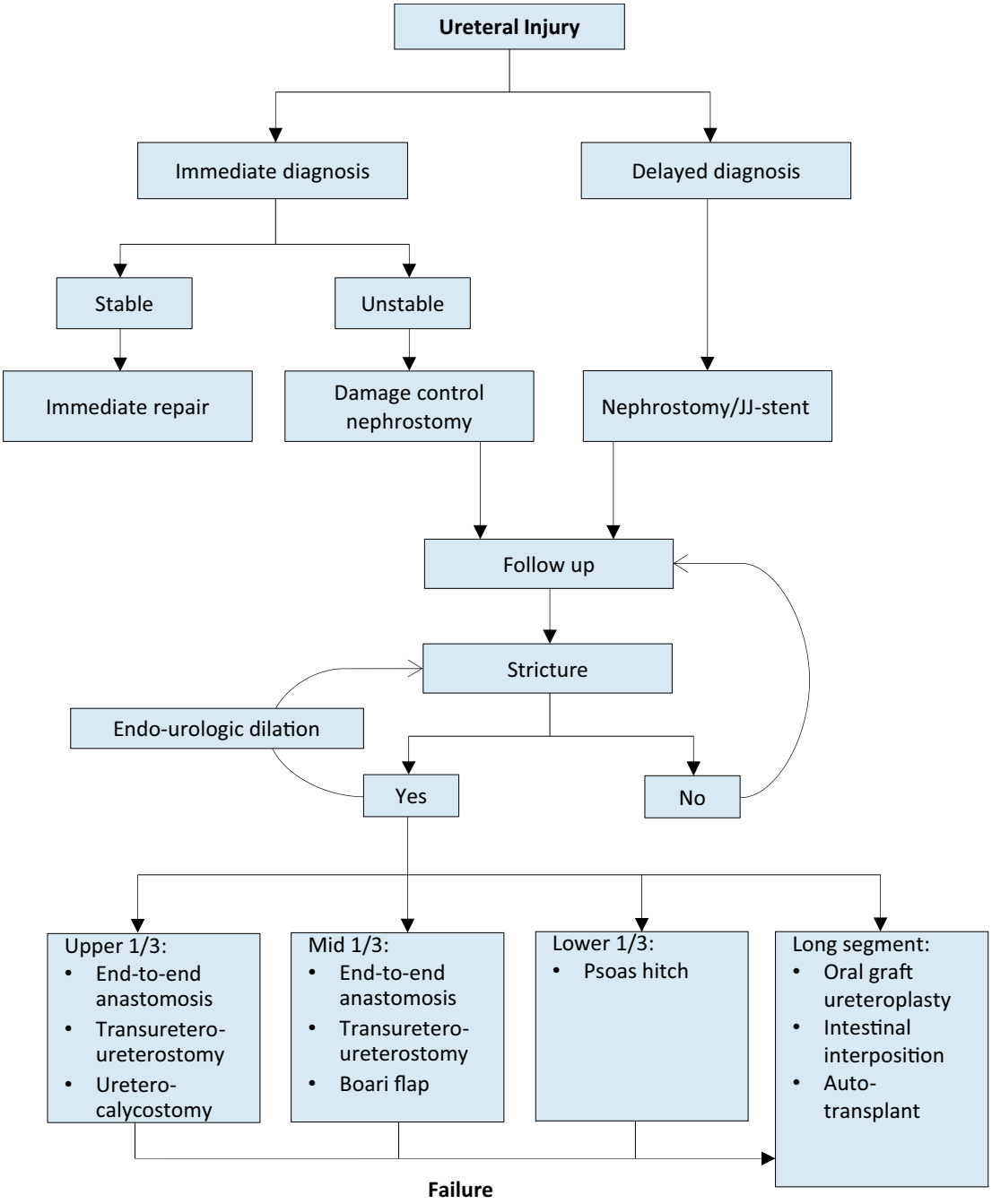
Summary of evidence	**LE**
Iatrogenic ureteral trauma is the most common cause of ureteral injury.	3
Gunshot wounds account for the majority of penetrating ureteral injuries, while MVAs account for most blunt injuries.	3
Ureteral trauma usually accompanies severe abdominal and pelvic injuries.	3
Haematuria is an unreliable and poor indicator of ureteral injury.	3
Pre-operative prophylactic stents do not prevent ureteral injury; however, they may assist in its detection.	2
Endo-urological treatment of small ureteral fistulae and strictures is safe and effective.	3
Major ureteral injury requires ureteral reconstruction following temporary urinary diversion.	3

Recommendations	Strength rating
Visually identify the ureters to prevent ureteral trauma during abdominal and pelvic surgery.	Strong
Beware of concomitant ureteral injury in all abdominal penetrating trauma, and in deceleration-type blunt trauma.	Strong
Use pre-operative prophylactic stents in high-risk cases.	Strong
Repair iatrogenic ureteral injuries recognised during surgery immediately.	Strong
Treat iatrogenic ureteral injuries with delayed diagnosis by nephrostomy tube/JJ stent urinary diversion.	Strong
Manage ureteral strictures by ureteral reconstruction according to the location and length of the affected segment.	Strong

*4.2.7 **Treatment algorithms***

Management of ureteral injuries

Figure 4.2.1: Management of ureteral injuries



4.3 Bladder Trauma

4.3.1 Classification

Bladder trauma is primarily classified according to the location of the injury: **intraperitoneal, extraperitoneal,** and **combined** intra-extraperitoneal [178], as it guides further management [179]. Bladder trauma is categorised by aetiology: **non-iatrogenic** (blunt and penetrating) and **iatrogenic** (external and internal).

4.3.2 Epidemiology, aetiology and pathophysiology

Motor vehicle accidents are the most common cause of blunt bladder injury, followed by falls and other accidents. The main mechanisms are pelvic crush and blows to the lower abdomen [124, 178, 180]. Most patients with blunt bladder injury have associated pelvic fractures (60-90%) and other intra-abdominal injuries (44-68.5%) [181, 182]. Pelvic fractures are associated with bladder injury in about 3% of cases [124, 183]; however, this can be as high as 26.5% in cases of severe pelvic injury [184]. Bladder injury is associated with urethral injury in 5-20% of cases [179, 182, 185].

The incidence of extraperitoneal (22.4-61.1%), and intraperitoneal (38.9-65.8%) injuries varies among series [186]. **Extraperitoneal injury** is almost always associated with pelvic fractures [180, 182]. It is usually caused by distortion of the pelvic ring, with shearing of the anterolateral bladder wall near the bladder base (at its fascial attachments), or by a contrecoup at the opposite side. The highest risk of bladder injury was found in disruptions of the pelvic circle with displacement > 1 cm, diastasis of the pubic symphysis > 1 cm, and pubic rami fractures [124, 179]. An isolated acetabular fracture is not likely to be associated with bladder injury [179, 182, 187]. Occasionally, the bladder is directly perforated by a sharp bony fragment [179].

Intraperitoneal injury is caused by a sudden rise in intravesical pressure of a distended bladder, secondary to a blow to the pelvis or lower abdomen. The bladder dome is the weakest point of the bladder and ruptures will usually occur there [179]. Penetrating injuries, mainly gunshot wounds, are rare except in conflict zones and violent urban areas [178, 188, 189]. Improvised explosive devices are the main cause of combat related bladder injuries in asymmetric warfare [190].

4.3.2.1 Iatrogenic bladder trauma (IBT)

The bladder is the urological organ that is most commonly affected by iatrogenic injury [191]. Table 4.3.1 shows the incidence of IBT during various procedures. **External IBT** occurs most often during obstetric and gynaecological procedures, followed by urological and general surgical operations [191]. Main risk factors are previous surgery, inflammation and malignancy [191]. Bladder perforations occur in up to 4.9% of mid-urethral sling operations for stress urinary incontinence in women. This rate is significantly lower in the obturator route compared to the retropubic route [192].

Internal IBT mainly occurs during transurethral resection of the bladder (TURB). Reported risk factors are larger tumours, older age, pre-treated bladders (previous TURB, intravesical instillations) and location at the bladder dome [193, 194]. Tumours at the lateral wall pose a risk factor because of the obturator jerk [195, 196]. Extraperitoneal perforations are more frequent than intraperitoneal perforations [194, 197], and perforations requiring intervention are rare (0.16-0.57%) [193].

Table 4.3.1: Incidence of iatrogenic bladder trauma during various procedures

Procedure	Percentage (%)
Obstetrics & Gynaecology	
Laparoscopic/Robotic radical hysterectomy (malignant) [198]	4.19-4.59
Abdominal radical hysterectomy (malignant) [198]	2.37
Hysterectomy laparoscopic/abdominal/vaginal (benign) [137, 199]	0.1-2.5
Caesarean delivery [200]	0.08-0.94
General surgery	
Abdominal cytoreductive surgery [201]	4.5
Rectal procedures [202]	0.27-0.41
Small/large bowel procedures [202]	0.12-0.14
Laparoscopic inguinal hernia repair [203]	0.04-0.14
Urology specific	
Transurethral resection of the bladder [204, 205]	3.5-58
Retropubic male sling [206]	8.0-19
Mid-urethral sling (retropubic route) [192, 207]	4.91-5.5
Transvaginal mesh surgery [208]	2.84
Pubovaginal sling [207]	2.8

Laparoscopic sacrocolpopexy [209]	1.9
Mid-urethral sling (transobturator route) [207]	1.61
Burch colposuspension [207, 210]	1.0-1.2
Native tissue colporrhaphy [208]	0.53

*4.3.3 **Diagnostic evaluation***

The principal sign of bladder injury is visible haematuria [179, 180]. Absolute indications for bladder imaging include: visible haematuria and a pelvic fracture [179] or non-visible haematuria combined with high-risk pelvic fracture (disruption of the pelvic circle with displacement > 1 cm or diastasis of the pubic symphysis > 1 cm) or posterior urethral injury [179]. Bladder trauma should also be suspected in patients with blunt urethral trauma and high Injury Severity Score (ISS) [211]. In the absence of these absolute indications, further imaging is based on clinical signs and symptoms including [179, 180, 188, 212]:

- inability to void or inadequate urine output;
- abdominal tenderness or distension due to urinary ascites, or signs of urinary ascites in abdominal imaging;
- uraemia and elevated creatinine level due to intraperitoneal re-absorption;
- entry/exit wounds at lower abdomen, perineum or buttocks in penetrating injuries.

Intra-operative signs of external iatrogenic bladder injury include: extravasation of urine, visible laceration, visible bladder catheter, and blood and/or gas in the urine bag during laparoscopy [200]. Direct inspection is the most reliable method of assessing bladder integrity [191]. Intravesical instillation of dye helps to detect smaller lesions [213]. If bladder perforation is close to the trigone, the ureteric orifices should be inspected [191, 200].

Internal bladder injury is recognised by cystoscopic identification of fatty tissue, dark space, or bowel [204]. It may also be detected by the inability to distend the bladder, low return of irrigation fluid, or abdominal distension [214].

Post-operatively, missed bladder trauma is diagnosed by haematuria, abdominal pain, abdominal distension, ileus, peritonitis, sepsis, urine leakage from the wound, decreased urinary output, or increased serum creatinine [191, 200]. An IBT during hysterectomy or caesarean delivery can result in vesico-vaginal or vesico-uterine fistulae [200, 215].

4.3.3.1 Cystography

Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for a suspected IBT in the post-operative setting [215, 216]. Both plain and CT cystography have a comparable sensitivity (90-95%) and specificity (100%) [180, 217]. However, CT cystography is superior in the identification of bony fragments in the bladder and bladder neck injuries, as well as concomitant abdominal injuries [179, 182].

Cystography must be performed using retrograde filling of the bladder with a minimum volume of 300-350 mL of dilute contrast material [216, 218]. Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury [180]. Intraperitoneal extravasation is visualised by free contrast medium in the abdomen outlining bowel loops or abdominal viscera [219]. Extraperitoneal bladder injury is typically diagnosed by flame-shaped areas of contrast extravasation in the peri-vesical soft tissues. Contrast medium in the vagina is a sign of vesico-vaginal fistula [215].

4.3.3.2 Cystoscopy

Cystoscopy is the preferred method for detection of intra-operative bladder injuries as it may directly visualise the laceration and can localise the lesion in relation to the position of the trigone and ureteral orifices [219]. A lack of bladder distension during cystoscopy suggests a large perforation. Cystoscopy is recommended to detect perforation of the bladder (or urethra) following retropubic sub-urethral sling operations [192, 210]. Routine intra-operative cystoscopy during other gynaecologic procedures is not recommended [220], although the threshold to perform it should be low in any suspected bladder injury.

4.3.3.3 Ultrasound

Ultrasound alone is insufficient in the diagnosis of bladder trauma, although it can be used to visualise intraperitoneal fluid or an extraperitoneal collection of fluid.

*4.3.4 **Prevention***

The risk of bladder injury is reduced by emptying the bladder by urethral catheterisation in every procedure where the bladder is at risk [213, 221]. Furthermore, the catheter's balloon can aid in identification of the bladder [213]. For tumours at the lateral wall, obturator nerve block or general anaesthesia with adequate muscle relaxation can reduce the incidence of internal IBT during TURB [196]. There is conflicting evidence

whether bipolar TURB can reduce the risk for an obturator jerk [195, 196]. The use of combat pelvic protection systems reduces the risk of bladder and other genitourinary injuries due to the blast mechanism of improvised explosive devices [190, 222].

*4.3.5 **Disease management***

4.3.5.1 Conservative management

Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis [194], is the standard treatment for an uncomplicated extraperitoneal injury due to blunt [179, 182, 185] or iatrogenic trauma [194].

Conservative treatment can also be chosen for uncomplicated intraperitoneal injury after TURB or other operations, but only in the absence of peritonitis and ileus [205, 219]. Placement of an intraperitoneal drain is advocated, especially when the lesion is larger [214, 223]. Penetrating extraperitoneal bladder injuries (only if minor and isolated) can also be managed conservatively [186, 212, 224].

4.3.5.2 Surgical management

Bladder closure is performed with absorbable sutures [186, 191]. There is no evidence that two-layer is superior to watertight single-layer closure [182, 186].

4.3.5.2.1 Blunt non-iatrogenic trauma

Most extraperitoneal ruptures can be treated conservatively; however, bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury or entrapment of the bladder wall necessitate surgical intervention [179, 225]. There is an increasing trend to treat pelvic ring fractures with open stabilisation and internal fixation with osteosynthetic material. During this procedure, an extraperitoneal rupture should be sutured concomitantly in order to reduce the risk of infection [226]. Likewise, an extraperitoneal rupture should be sutured during surgical exploration for other injuries, in order to decrease the risk of complications and to reduce recovery time [185].

Intraperitoneal ruptures should always be managed by surgical repair [179, 182] because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death [181]. Abdominal organs should be inspected for possible associated injuries and urinomas must be drained if detected. Laparoscopic suturing of the intraperitoneal rupture is also possible [180].

4.3.5.2.2 Penetrating non-iatrogenic trauma

Penetrating bladder injury is managed by emergency exploration, debridement of devitalised bladder wall and primary bladder repair [188, 189]. A midline exploratory cystotomy is advised to inspect the bladder wall and the distal ureters [186, 188]. In gunshot wounds, there is a strong association with intestinal and rectal injuries, usually requiring faecal diversion [188, 212]. Most gunshot wounds are associated with two transmural injuries (entry and exit wounds) and the bladder should be carefully checked for these two lesions [188]. As the penetrating agent (bullet, knife) is not sterile, antibiotic treatment is advised [189].

4.3.5.2.3 Iatrogenic bladder trauma

Perforations recognised intra-operatively are primarily closed [227]. Bladder injuries not recognised during surgery or internal injuries should be managed according to their location. The standard of care for intraperitoneal injuries is surgical exploration and repair [219]. If surgical exploration is performed after TURB, the bowel must be inspected to rule out concomitant injury [193]. For extraperitoneal injuries, exploration is only needed for perforations complicated by symptomatic extravesical collections. It requires drainage of the collection, with or without closure of the perforation [228]. If bladder perforation is encountered during mid-urethral sling or transvaginal mesh procedures, sling re-insertion and urethral catheterisation (two to seven days) should be performed [229].

*4.3.6 **Follow-up***

Continuous bladder drainage is required to prevent elevated intravesical pressure and to allow the bladder to heal [191, 230]. Conservatively treated bladder injuries (traumatic or external IBT) are followed up by cystography to rule out extravasation and ensure proper bladder healing [179]. The first cystography is planned approximately ten days after injury [186]. In case of ongoing leakage, cystoscopy should be performed to rule out bony fragments in the bladder, and a second cystography is warranted one week later [179].

After operative repair of a simple injury in a healthy patient, the catheter can be removed after five to ten days without cystography [230, 231]. In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g. steroids, malnutrition) cystography is advised [186, 230]. For conservatively treated internal IBT, catheter drainage, lasting five days for extraperitoneal and seven days for intraperitoneal perforations, is proposed [194, 197].

4.3.7 *Summary of evidence and recommendations for bladder injury*

Summary of evidence	LE
The combination of pelvic fracture and visible haematuria is highly suggestive of bladder injury.	3
Cystography is the preferred diagnostic modality for non-iatrogenic bladder injury and for suspected IBT in the post-operative setting.	3
Cystography must be performed using retrograde filling of the bladder with a minimum volume of 300-350 mL of dilute contrast material. Passive bladder filling by clamping the urinary catheter during the excretory phase of CT or IVP is not sufficient to exclude bladder injury.	3
The risk of bladder perforation during mid-urethral sling operations for stress urinary incontinence is lower for the obturator route compared to the retropubic route.	1a
Conservative treatment, which comprises of clinical observation, continuous bladder drainage and antibiotic prophylaxis, is the standard treatment for an uncomplicated extraperitoneal injury due to blunt trauma.	3
In extraperitoneal bladder injury with either bladder neck involvement, bone fragments in the bladder wall, concomitant rectal or vaginal injury, or entrapment of the bladder wall, surgical intervention is necessary in order to decrease the risk of complications and to reduce recovery time.	3
Intraperitoneal bladder trauma is managed by surgical repair because intraperitoneal urine extravasation can lead to peritonitis, intra-abdominal sepsis and death.	3
Conservative treatment is suitable for uncomplicated intraperitoneal injury during endo-urological procedures, in the absence of peritonitis and ileus.	3
In cases of complex injury (trigone involvement, ureteric re-implantation) or risk factors of impaired wound healing (e.g. steroids, malnutrition) cystography is advised after bladder repair.	2a

Recommendations	Strength rating
Perform cystography in the presence of visible haematuria and pelvic fracture.	Strong
Perform cystography in case of suspected iatrogenic bladder injury in the post-operative setting.	Strong
Perform cystography with active retrograde filling of the bladder with dilute contrast (300-350 mL).	Strong
Perform cystoscopy to rule out bladder injury during retropubic sub-urethral sling procedures.	Strong
Manage uncomplicated blunt extraperitoneal bladder injuries conservatively.	Weak
Manage blunt extraperitoneal bladder injuries operatively in cases of bladder neck involvement and/or associated injuries that require surgical intervention.	Strong
Manage blunt intraperitoneal injuries by surgical exploration and repair.	Strong
Manage small uncomplicated intraperitoneal bladder injuries during endoscopic procedures conservatively.	Weak
Perform cystography to assess bladder wall healing after repair of a complex injury or in case of risk factors for wound healing.	Strong

4.4 Urethral Trauma

4.4.1 *Epidemiology, aetiology and pathophysiology*

4.4.1.1 *Anterior male urethral injury*

The bulbar urethra is the most common site affected by **blunt** trauma. In bulbar injuries, the bulb is compressed against the pubic symphysis, resulting in rupture of the urethra at the site of compression [232]. Possible mechanisms are straddle injuries or kicks to the perineum. A penile fracture can be complicated by a urethral injury in approximately 15% of cases [233, 234]. **Penetrating** anterior injuries are rare and are usually caused by gunshot wounds, stab wounds, dog bites, impalement or penile amputations [232, 235]. Depending on the affected segment, penetrating injuries are usually associated with penile, testicular and/or pelvic injuries [235]. Insertion of **foreign bodies** is another rare cause of anterior injury. It is usually a result of autoerotic stimulation or may be associated with psychiatric disorders [236].

Iatrogenic injury is the most common type of urethral trauma [237]. The incidence of male urethral injury during transurethral catheterisation is 13.4 per 1,000 catheters inserted [238]. Injuries can occur due to creation of a false passage by the tip of the catheter or inadvertent inflation of the anchoring balloon in the urethra [238]. The importance of catheter insertion training programmes [239, 240] and the implementation of difficult urinary catheterisation protocols [241], to prevent urethral injury during transurethral catheterisation, have been demonstrated. Preliminary data suggests that guidewire led catheter insertion, or use of a safety

valve for balloon inflation may prevent urethral trauma in difficult catheterisation cases [242, 243]. During penile prosthesis insertion, the risk of urethral perforation is 0.1-4%. Proximal urethral injuries are more common than distal ones [244].

4.4.1.2 Posterior male urethral injuries

Blunt posterior urethral injuries are almost exclusively related to pelvic fractures and the risk increases with fracture configuration severity [245]. These injuries are referred to as pelvic fracture urethral injuries (PFUI) [232], and are mainly caused by MVAs [246]. Pelvic fracture urethral injuries are divided into partial or complete ruptures [245, 246]. In complete ruptures, there is a gap between the disrupted ends of the urethra, which fills up with scar tissue. There is no urethral wall in the scarred space and any lumen represents a fistulous tract between the urethral stumps [247]. Injuries of the bladder neck and prostate are rare and mostly occur at the anterior midline of both the bladder neck and prostatic urethra [248]. It is highly uncommon to find a complete transection of the bladder neck or an avulsion of the anterior part of the prostate [248]. Concomitant injuries to the head, thorax, abdomen and/or spine are frequent (up to 66%) [246].

Penetrating injuries of the pelvis, perineum or buttocks (mainly gunshot wounds) can also damage the posterior urethra, but are extremely rare in the civilian setting [245]. There is a high probability of associated injuries (approx. 90%), mainly intra-abdominal [188].

The associated injuries which occur with both blunt and penetrating posterior urethral injuries can be life-threatening, and if so, will govern the patient's assessment and treatment [246]. Delayed morbidities of posterior urethral injuries include strictures, incontinence and erectile dysfunction, all of which may have a detrimental effect on the patient's quality of life [249]. The pooled estimate for the proportion of patients with erectile dysfunction following PIFU is 34% [250].

Iatrogenic injury has been reported with transanal total mesorectal excision in 1-11% of cases. This injury is usually partial and located at the membranous urethra [251].

4.4.1.3 Female urethral injuries

Birth related injuries to the female urethra are rare and consist of minor (peri)urethral lacerations during vaginal delivery. Pelvic fractures are the main cause of blunt trauma [252]; however, PFUIs in females are rare and less common than in males [245]. This is usually attributed to the flexibility provided by the vagina and the greater inherent elasticity of the female urethra [252], it may also be the result of less severe and more frequent stable pelvic fractures in females [179, 246]. In unstable pelvic fractures in females, a high suspicion for a urethral injury should be maintained [252]. Female urethral injuries are classified into two types: longitudinal or partial (most frequent) injuries and transverse or complete injuries [252]. Concomitant bladder or vaginal injury is possible; therefore, females are at risk of developing urinary incontinence and urethrovaginal fistula [246, 252].

Insertion of a synthetic sub-urethral sling for the treatment of female stress urinary incontinence is complicated by an intra-operative urethral injury in 0.2-2.5% of cases [253] and is an important cause of **iatrogenic** urethral injury.

*4.4.2 **Evaluation***

4.4.2.1 Clinical signs

Blood at the meatus is the cardinal sign, but the absence of it doesn't rule out a urethral injury [179, 246]. Inability to void (with a palpable distended bladder) is another classic sign and is often associated with a complete rupture [246, 247]. Haematuria and pain on urination may be present in incomplete ruptures. Urinary extravasation and bleeding may result in scrotal, penile and/or perineal swelling and ecchymosis, depending on the location and extent of the trauma. The presentation of these clinical symptoms may be delayed (> 1 hour)[247].

Rectal examination should always be done to exclude an associated rectal injury (up to 5% of cases), and may reveal a 'high-riding' prostate, which is an unreliable finding [179, 247]. Failure to detect a rectal injury can cause significant morbidity and even mortality. A rectal injury is suggested by blood on the examining finger and/or a palpable laceration [179]. Another sign of urethral injury is difficulty or inability to pass a urethral catheter [179, 247].

A female urethral injury should be suspected from the combination of a (unstable) pelvic fracture with blood at the vaginal introitus, vaginal laceration, haematuria, urethrorrhagia, labial swelling, urinary retention or difficulties passing a urethral catheter [179, 249]. Vaginal examination is indicated to assess vaginal lacerations [179, 249].

4.4.2.2 Urethrography

Retrograde urethrography (RUG) is the standard in the early evaluation of a male urethral injury [179, 254] and is conducted by injecting 20-30 mL of contrast material while occluding the meatus. Films should be taken in a 30° oblique position. In patients with PFUI, it is important to move the X-ray beam to the 30° angle rather than the patient [246]. In an unstable patient, RUG should be postponed until the patient has been stabilised [179, 188].

During RUG, any extravasation outside the urethra is pathognomonic for urethral injury [247]. A typical image for incomplete rupture shows extravasation from the urethra which occurs while the bladder is still filling. A complete rupture is suggested by massive extravasation without bladder filling [246]. Although RUG is able to reliably identify the site of injury (anterior vs. posterior), the distinction between a complete and partial rupture is not always clear [246, 255]. Therefore, any proposed classification system based on RUG is not reliable [246, 255]. In females, the short urethra and vulvar oedema makes adequate urethrography nearly impossible [256].

Prior to deferred treatment, a combination of RUG and antegrade cysto-urethrography is the standard to evaluate site and extent of the urethral stenosis, and to evaluate the competence of the bladder neck [246].

4.4.2.3 Cysto-urethroscopy

Flexible cysto-urethroscopy is a valuable alternative to diagnose an acute urethral injury and may distinguish between complete and partial rupture [254]. Flexible cysto-urethroscopy is preferred to RUG in suspected penile fracture-associated urethral injury as RUG is associated with a high false-negative rate [257, 258]. In females, where the short urethra often precludes adequate radiological visualisation, cysto-urethroscopy and vaginoscopy are the diagnostic modalities of choice [179, 252]. If, prior to deferred treatment, the competence of the bladder neck is not clear upon antegrade cysto-urethrography, a suprapubic cystoscopy is advised [246].

4.4.2.4 Ultrasound and magnetic resonance imaging

In the acute phase, US scanning is used for guiding the placement of a suprapubic catheter [246]. In complex PFUIs, MRI before deferred treatment provides valuable additional information, which can help to determine the most appropriate surgical strategy [259]. This information includes a better estimation of the length of the distraction defect, degree of prostatic displacement and presence/absence of a false passage [259].

*4.4.3 **Disease Management***

4.4.3.1 Male anterior urethral injuries

4.4.3.1.1 Immediate exploration and urethral reconstruction

This is indicated for penile fracture related injuries [260] and non-life threatening penetrating injuries [249]. Small lacerations can be repaired by simple closure [234]. Complete ruptures without extensive tissue loss are treated with anastomotic repair [234, 235]. Only 2% of cases will develop a urethral stricture after immediate urethral reconstruction for penile fracture [260]. In the case of longer defects or apparent infection (particularly bite wounds), a staged repair with urethral marsupialisation is needed [254]. Penetrating injuries require peri- and post-operative antibiotic treatment [261].

Immediate urethroplasty has been performed in blunt injuries. The long term-outcomes (patency rate, potency rate) of patients treated with immediate urethroplasty is similar to these initially treated with suprapubic diversion and delayed urethroplasty [262]. The main advantage of performing immediate urethroplasty is that this strategy significantly reduces the time to spontaneous voiding from two to six months to three weeks on average [262, 263]. Spongiosal contusion and haematoma during immediate urethroplasty will make the operation technically more demanding; therefore, immediate urethroplasty should be performed by a dedicated urethral surgeon [263].

Perforation of the distal urethra during penile prosthesis insertion needs to be repaired over a catheter; in this instance the initial procedure should be abandoned [264].

4.4.3.1.2 Urinary diversion

Blunt anterior urethral injuries are associated with spongiosal contusion. Evaluation of the limits of urethral debridement in the acute phase might be difficult and as a consequence, it is reasonable to start with urinary diversion only [254].

If urinary diversion is performed, the therapeutic options are suprapubic diversion or a trial of early endoscopic re-alignment with transurethral catheterisation [254]; there is conflicting evidence as to which intervention is superior [262, 263, 265]. Urinary diversion is maintained for one to two weeks for partial ruptures and three weeks for complete ruptures [254, 265]. A review of 49 Chinese studies (1,015 patients), reported a 57% (range: 0-100%) success rate for endoscopic re-alignment of blunt anterior injuries [262]. The wide range in success rate most likely reflects a mix of partial and complete ruptures which was not further specified in the review. For complete ruptures, urinary diversion on its own is unlikely to result in a successful outcome (0-25% patency rate) [263, 265].

Transurethral or suprapubic urinary diversion are treatment options for iatrogenic or life-threatening penetrating injuries [249, 266]. Minor iatrogenic urethral injuries and urethral contusions do not require urinary diversion [3].

4.4.3.2 Male posterior urethral injuries

4.4.3.2.1 Emergency room management

As these injuries are usually associated with other severe injuries, resuscitation and immediate treatment of life-threatening injuries have absolute priority [246]. Penetrating injuries especially have a very high likelihood of associated injuries requiring immediate exploration [188, 267]. There is no urgency to treat the urethral injury and urinary diversion is not essential during the first hours after trauma [247]; however, it is preferable to establish early urinary diversion to:

- monitor urinary output, since this is a valuable sign of the haemodynamic condition and the renal function of the patient;
- treat symptomatic retention if the patient is still conscious;
- minimise urinary extravasation and its secondary effects, such as infection and fibrosis [246].

Insertion of a suprapubic catheter is an accepted practice in urgent situations [247, 267]. However, insertion of a suprapubic catheter is not without risk, especially in the unstable trauma patient where the bladder is often displaced by a pelvic haematoma or because of poor bladder filling due to haemodynamic shock or concomitant bladder injury. In these circumstances, an attempt at urethral catheterisation can be carried out by experienced personnel. It is extremely unlikely that the gentle passage of a urethral catheter will do any additional damage [246]. If there is any difficulty, a suprapubic catheter should be placed under US guidance or under direct vision, for example, during laparotomy for associated injuries [246]. Suprapubic catheter placement does not increase the risk of infectious complications in patients undergoing internal fixation to stabilise a pelvic fracture [268]. Therefore, the assertion that suprapubic catheter placement would increase the risk of orthopaedic hardware infection and subsequent explantation is not justified [268].

4.4.3.2.2 Early urethral management (less than six weeks after injury)

For partial injuries, urinary diversion (suprapubic or transurethral) is sufficient as these injuries can heal without significant scarring or obstruction [247, 249]. A complete injury will not heal, and formation of an obliterated segment is inevitable in case of suprapubic diversion alone [247, 249]. To avoid this obliteration and a long period of suprapubic diversion followed by deferred urethroplasty, the urethral ends can be sutured (urethroplasty) or approximated over a transurethral catheter (re-alignment).

4.4.3.2.2.1 Immediate urethroplasty

Urethroplasty within 48 hours after injury is difficult because of poor visualisation and the inability to accurately assess the degree of urethral disruption, due to extensive swelling and ecchymosis, which may result in extensive unjustified urethral debridement. Another problem is the risk of severe bleeding (average 3 L) following entry into the pelvic haematoma [246]. In addition, with high rates of impotence (23%), incontinence (14%) and strictures (54%), urethroplasty within 48 hours is not indicated [246].

4.4.3.2.2.2 Early urethroplasty

Urethroplasty can be performed after two days and up to six weeks after the initial injury, if associated injuries have been stabilised, the distraction defect is short, the perineum is soft and the patient is able to lie down in the lithotomy position [269, 270]. This avoids a long period of suprapubic diversion with its discomfort and complications [269, 270]. As the results (complications, stricture recurrence, incontinence and impotence) are equivalent to delayed urethroplasty [270-272], early urethroplasty might be an option for patients fulfilling the above-mentioned criteria.

Lacerations (blunt or penetrating) at the bladder neck and prostatic urethra are a specific entity: they will never heal spontaneously, will cause local cavitation (presenting a source of infection) and compromise the intrinsic sphincter mechanism (with increased risk of urinary incontinence) [248]. They must be reconstructed as soon as possible [249, 255, 267]. For penetrating injuries with severe lesions to the prostate, prostatectomy (bladder neck sparing) must be performed [267].

4.4.3.2.2.3 Early re-alignment

Early re-alignment can be performed when a stable patient is on the operating table for other surgery or as a stand-alone procedure in the absence of concomitant injuries [188, 273]. In a partial injury, re-alignment, and transurethral catheterisation avoids extravasation of urine in the surrounding tissues reducing the inflammatory response. In complete injuries, the aim of re-alignment is to correct severe distraction injuries rather than to prevent a stricture [249, 274].

Re-alignment can be done by an open or endoscopic technique [274, 275]. The open technique is associated with longer operation times, more blood loss and longer hospital stays; as such, endoscopic re-alignment is now preferred [262]. Using a flexible/rigid cystoscope and biplanar fluoroscopy, a guidewire is placed inside the bladder under direct visual control, over this, a catheter is placed. If necessary, two

cystoscopes can be used: one retrograde (per urethra) and one antegrade (suprapubic route through the bladder neck) [246]. The duration of catheterisation is three weeks for partial and six weeks for complete ruptures with voiding urethrography upon catheter removal [246]. It is important to avoid traction on the balloon catheter as it can damage the remaining sphincter mechanism at the bladder neck [246].

With contemporary endoscopic re-alignment procedures, stricture formation is reduced to 44-49% [274, 275] compared to a 89-94% stricture rate with suprapubic diversion [275, 276]. There is no evidence that early re-alignment increases the risk of urinary incontinence (4.7-5.8%) or erectile dysfunction (16.7-20.5%) [275, 276].

Another potential benefit of early re-alignment is that when a stricture occurs it will be shorter and therefore, easier to treat. For short, non-obliterative strictures following re-alignment, direct vision urethrotomy can be performed. Approximately 50% of strictures after endoscopic re-alignment can be treated endoscopically [274]. However, repetitive endoscopic procedures in case of stricture formation might delay the time to definitive cure and can increase the incidence of adverse events (false passage, abscess formation) [277, 278]. In light of this, repetitive endoscopic treatments after failed re-alignment are not recommended; instead, urethroplasty must be performed.

Koraitim *et al*., found a shorter stricture length after early (open) re-alignment and as a consequence, a tendency for less complex manoeuvres to be needed to allow for a tension-free anastomosis during urethroplasty [279]. On the other hand, Tausch *et al*., reported an equal stricture length and no greater facilitation of urethroplasty after failed endoscopic re-alignment compared to suprapubic diversion only [277]. The proposed benefit is thus highly questionable. Furthermore, there is conflicting evidence as to whether failed early re-alignment jeopardises the success of definitive urethroplasty [246].

Differences between series in the rates of incontinence, impotence and re-stricture can be explained by differences in patient selection (severe vs. less severe trauma), a mix of partial and complete ruptures, and differences in follow-up duration. Furthermore, these differences make the comparison with other techniques difficult, especially with urethroplasty [179, 274].

4.4.3.2.3 Deferred management (greater than three months after injury)

The standard treatment remains deferred urethroplasty [13, 14]. In the case of a complete rupture, treated with an initial period of three months suprapubic diversion, obliteration of the posterior urethra is almost inevitable [247]. Endoscopic treatment of a complete obliteration is not successful [246]. After at least three months of suprapubic diversion, the pelvic haematoma is nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [269] and the patient is clinically stable and able to lie down in the lithotomy position [254, 269]. Associated life-threatening injuries often preclude early management of penetrating membranous urethral injuries. In those cases, suprapubic diversion with delayed urethroplasty is also advised [17, 25, 26]. Perineal anastomotic repair is the surgical technique of choice, but a combined abdominoperineal approach is necessary in rare cases of concomitant bladder neck injury or recto-urethral fistula [280].

The overall success rate for deferred urethroplasty is 86% [246]. Deferred urethroplasty does not significantly affect erectile function [281]. Although, a small proportion (< 7%) of patients report *de novo* erectile dysfunction after delayed urethroplasty, others (6-20%) have recovery of erectile dysfunction after delayed urethroplasty [246]. Incontinence is rare with deferred urethroplasty (approximately 5%), and is usually due to incompetence of the bladder neck [246]. The assessment of sexual function and the decision on definitive treatment (e.g. penile prosthesis), should be undertaken two years after the trauma due to the potential return of potency within that time [255, 282].

4.4.3.2.4 Iatrogenic posterior injuries

Urethral defects during transanal total mesorectal excision were repaired by direct suture repair via a transperineal approach in a small case series (n=32). Despite direct repair, 26% developed complications including urethral stricture, urethral dehiscence, recto-urethral fistula, and recto-perineal fistula. No evidence on other strategies is available [251].

4.4.3.3 Female urethral injuries

Emergency room management of PFUIs in females is the same as in males (section 4.4.3.2.1); however, subsequent management differs. Treatment options are [252]:

- **Early realignment:** This is associated with a high stricture and fistula rate.
- **Early repair (less than or equal to seven days):** Complication rate is the lowest with early repair; therefore, this strategy is preferred once the patient is haemodynamically stable [249, 252].
- **Delayed repair (greater than seven days):** Delayed repair often requires complex abdominal or combined abdominal-vaginal reconstruction with elevated risk of urinary incontinence and vaginal stenosis.

The approach (vaginal, abdominal or combined) for early repair depends on the location of the injury [252]. Proximal and mid-urethral disruptions require immediate exploration and primary repair using the retropubic and transvaginal routes, respectively, with primary suturing of the urethral ends or urethral laceration. Concomitant vaginal lacerations are repaired (two-layer closure) transvaginally at the same time [252]. Distal urethral injuries can be left hypospadiac since they do not disrupt the sphincter mechanism, but a concomitant vaginal laceration must be closed [179, 256]. In case of urethral injury during synthetic sub-urethral sling insertion, immediate repair is warranted with abandonment of sling insertion [253].

Table 4.4.1: Complication rates for different treatment strategies for PFUIs in females [252]

Type of repair	Stricture (%)	Fistula (%)	Incontinence (%)	Vaginal stenosis (%)	Need for permanent urinary diversion (%)
Early realignment	59	13	0	0	0
Early repair	3	6	9	0	3
Delayed repair	3	4	31	4	7

4.4.4 Summary of evidence and recommendations for the evaluation and management of urethral trauma

Summary of evidence	LE
Implementing training programmes on urinary catheter insertion for personnel involved with urethral catheterisation significantly improves the rate of catheter-related complications.	2b
In males, a urethral injury is detected as contrast extravasation during urethrography or as a mucosal laceration during cysto-urethroscopy.	3
As opposed to cysto-urethroscopy, voiding cysto-urethrography will miss a female urethral injury in approximately 50% of cases.	3
Transurethral or suprapubic urinary diversion are the treatment options for iatrogenic injuries.	3
With urinary diversion (suprapubic or transurethral catheter) satisfactory urethral luminal re-canalisation may occur after partial blunt anterior urethral ruptures.	3
Complete blunt anterior urethral ruptures are unlikely to be cured by urinary diversion alone, whereas immediate urethroplasty has an equal success rate compared to delayed urethroplasty. The main advantage of immediate urethroplasty is to reduce the time to spontaneous voiding.	3
If PFUIs are associated with life-threatening injuries, urethral management has no priority and urinary diversion with either urethral or suprapubic catheterisation is sufficient initially.	3
With early endoscopic re-alignment the stricture rate is reduced to 44-49% without increased risk of incontinence or erectile dysfunction.	3
Repetitive endoscopic treatments after failed re-alignment delay the time to definitive cure and increase the incidence of adverse events.	3
For partial posterior injuries, urinary diversion (suprapubic or transurethral) is sufficient as these injuries might heal without significant scarring or obstruction.	3
Immediate urethroplasty (< 48 hours) in male PFUI is associated with a higher risk of bleeding, stricture, incontinence and impotence rates compared to delayed urethroplasty.	3
In selected patients for male PFUI, early urethroplasty (two days to six weeks) is associated with similar stricture, incontinence and impotence rates compared to delayed urethroplasty.	3
Suprapubic diversion with delayed urethroplasty in male PFUI with complete urethral disruption is associated with a 86% stricture free success rate and with no significant impact on erectile function and urinary continence.	2a
Early repair in female PFUI has the lowest complication rate.	3

Recommendations	Strength rating
Provide appropriate training to reduce the risk of traumatic catheterisation.	Strong
Evaluate male urethral injuries with flexible cysto-urethroscopy and/or retrograde urethrography.	Strong
Evaluate female urethral injuries with cysto-urethroscopy and vaginoscopy.	Strong
Treat iatrogenic anterior urethral injuries by transurethral or suprapubic urinary diversion.	Strong
Treat partial blunt anterior urethral injuries by suprapubic or urethral catheterisation.	Strong

Treat complete blunt anterior urethral injuries by immediate urethroplasty, if surgical expertise is available, otherwise perform suprapubic diversion with delayed urethroplasty.	Weak
Treat pelvic fracture urethral injuries (PFUIs) in haemodynamically unstable patients by transurethral or suprapubic catheterisation initially.	Strong
Perform early endoscopic re-alignment in male PFUIs when feasible.	Weak
Do not repeat endoscopic treatments after failed re-alignment for male PFUI.	Strong
Treat partial posterior urethral injuries initially by suprapubic or transurethral catheter.	Strong
Do not perform immediate urethroplasty (< 48 hours) in male PFUIs.	Strong
Perform early urethroplasty (two days to six weeks) for male PFUIs with complete disruption in selected patients (stable, short gap, soft perineum, lithotomy position possible).	Weak
Manage complete posterior urethral disruption in male PFUIs with suprapubic diversion and deferred (at least three months) urethroplasty.	Strong
Perform early repair (within seven days) for female PFUIs (not delayed repair or early re-alignment).	Strong

*4.4.5 **Treatment algorithms***

Management of anterior and posterior urethral injuries in men

Figure 4.4.1: Management of anterior urethral injuries in men

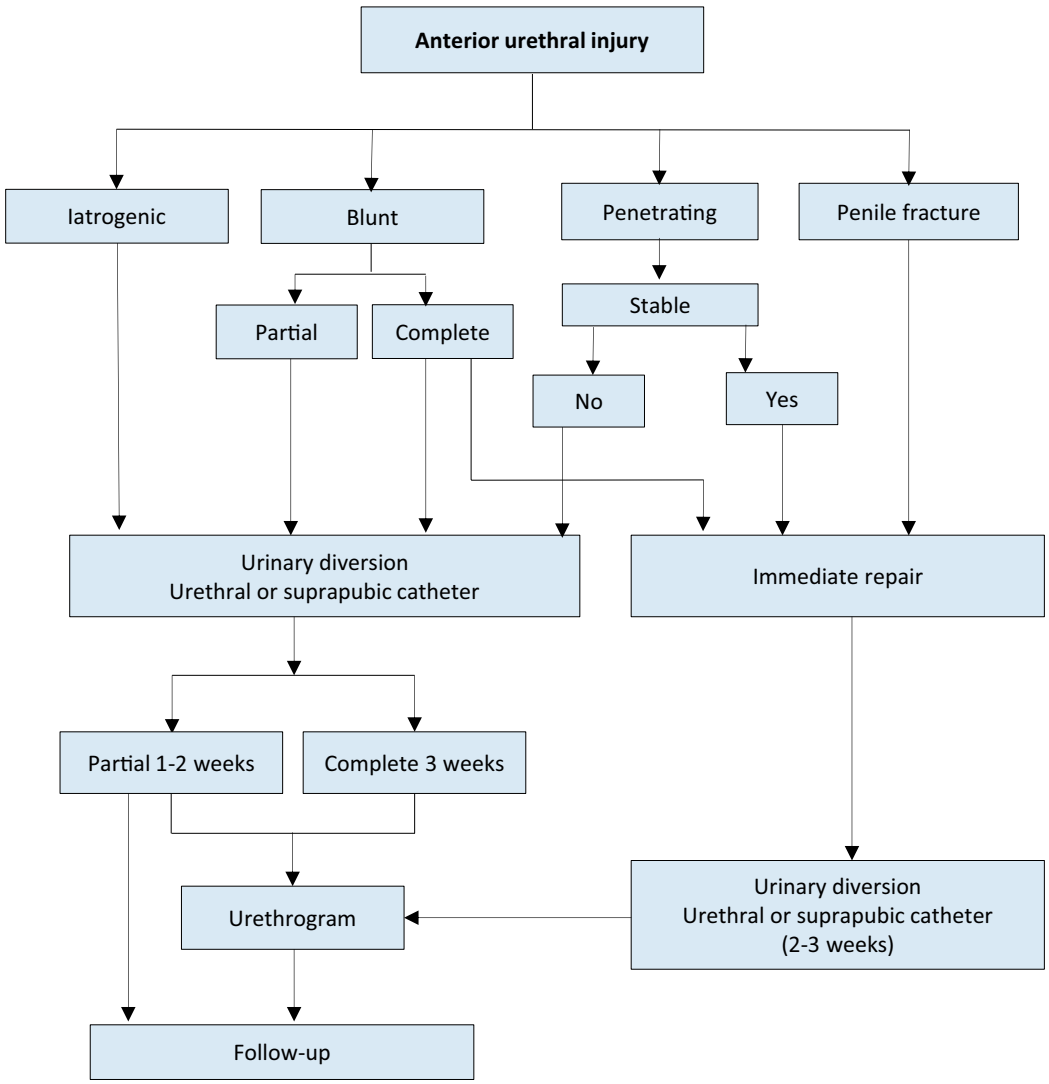
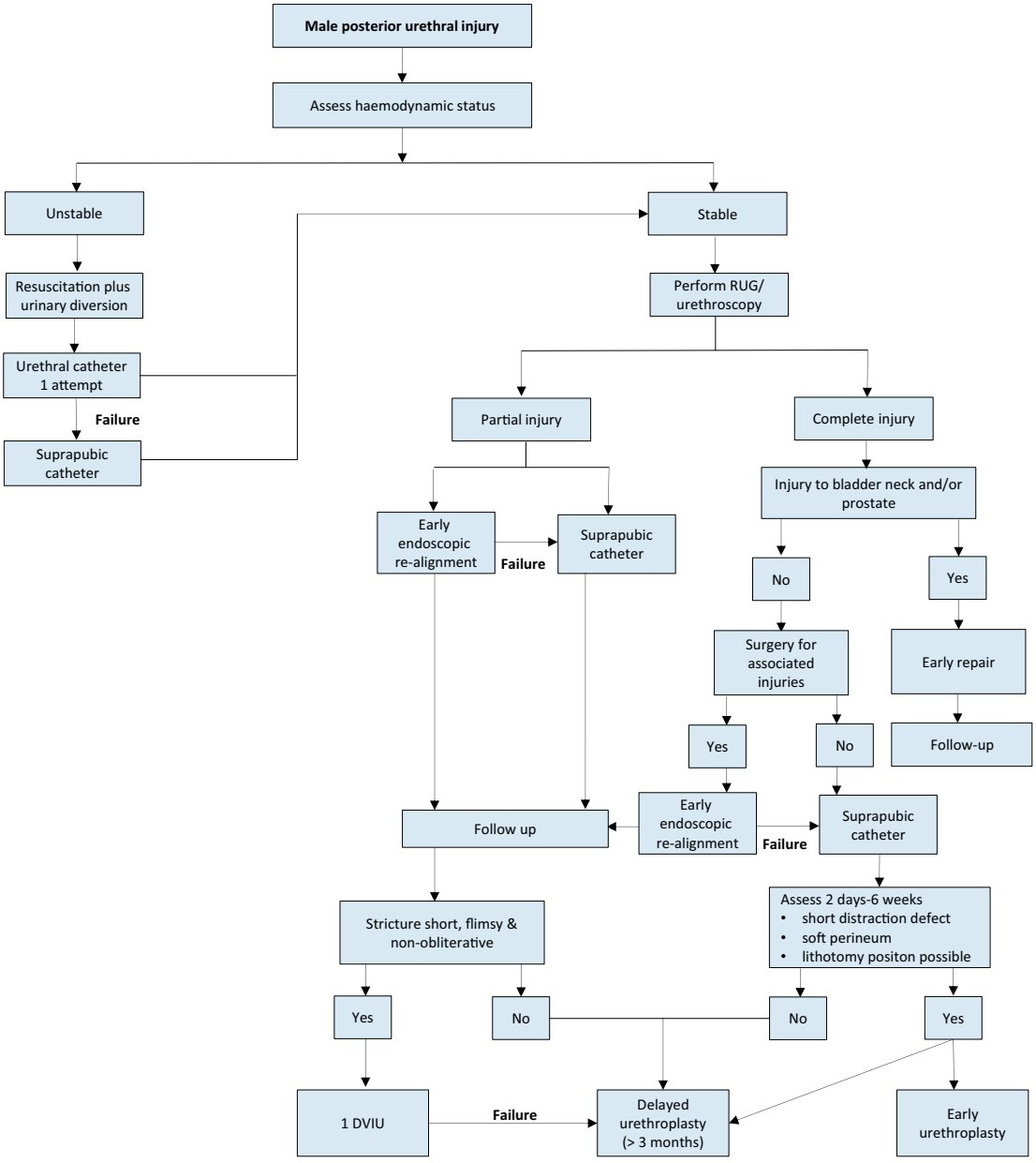


Figure 4.4.2: Management of posterior urethral injuries in men



RUG = retrograde urethrography; DVIU = direct visual internal urethrotomy.

4.5 Genital Trauma

4.5.1 Epidemiology, aetiology and pathophysiology

Of all urological injuries, 33-66% involve the external genitalia [283]. Genital trauma is much more common in males than in females, especially between the ages of 15 and 40 years. This is due to anatomical differences, increased frequency of MVAs and increased participation in physical sports, war and crime [284]. The risk of associated injuries to neighbouring organs (bladder, urethra, vagina, rectum and bowel), after blunt trauma is higher in females than in males.

Genital trauma is commonly caused by blunt injuries (80%). In males, blunt genital trauma frequently occurs unilaterally with approximately 1% presenting as bilateral scrotal or testicular injuries [285]. Any kind of contact sport, without the use of protective aids, may be associated with genital trauma. Off-road cycling, motor biking (especially on motorbikes with a dominant petrol tank), rugby, football and hockey are all activities associated with blunt testicular trauma [286-289]. Penetrating injuries are most commonly caused by firearms (75.8%) with the majority requiring surgical intervention [290, 291].

Accidents during sexual intercourse can also cause genital trauma; men of younger age are the most affected. The major pathologies are penile fractures, strangulation, necrosis, and assorted injuries from various sexual practices [292, 293].

The most important presentation of blunt penile trauma is penile fracture. The most common causes are sexual intercourse, forced flexion (taqaandan), masturbation and rolling over in 46%, 21%, 18% and 8.2%, respectively [294]. It has also been reported that penile fracture patients have a significantly higher rate of substance abuse [295]. The usual mechanism of injury is when the penis slips out of the vagina and strikes against the symphysis pubis or perineum. Sixty per cent of cases occur during consensual intercourse [296], with penile fracture more likely in certain positions [297]. Penile fracture is caused by rupture of the cavernosal tunica albuginea, and may be associated with subcutaneous haematoma and lesions of the corpus spongiosum or urethra in 10-22% [298-300]. Genital injury is prevalent (42%) after sexual abuse [301].

Although animal bites are common, bites injuring the external genitalia are rare. Wounds are usually minor, but have a risk of wound infection.

Gunshot injuries to the external genitalia are relatively uncommon and are usually not life-threatening; however, they can have a significant impact on quality of life. About 40-60% of all penetrating genito-urinary lesions involve the external genitalia [302, 303], 35% of these are gunshot wounds [285]. In a series of wartime injuries, the majority were caused by improvised explosive devices and other explosive ordinance, while smaller numbers of injuries were due to gunshot injuries [304]. In both males and females, penetrating injuries affect multiple organs in 70% of patients. In males, penetrating scrotal injuries affect both testes in 30% of cases compared with 1% in blunt injuries [285, 305]. Self-mutilation of the external genitalia has also been reported in psychotic patients and transsexuals [306]. Genital burns are rare in isolation and are usually due to industrial flames or chemicals [307]. Both male and female genital piercings increase the risk for unexpected genital trauma [308].

Traumatic dislocation of the testicle rarely occurs and is most common in victims of MVAs [309-312]. Bilateral dislocation of the testes has been reported in up to 25% of cases [310]. Testicular rupture is found in approximately 50% of cases of direct blunt scrotal trauma [313, 314]. It may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea. A force of approximately 50 kg is necessary to cause testicular rupture [315]. Most penile avulsion injuries are self-inflicted, but some are a result of industrial accidents or assault.

Coital injury of the female genital tract can happen during consensual sexual intercourse. Up to 35% of all genital injuries in women are sustained during their first sexual contact. The most frequently found injuries are lacerations [316]. Blunt trauma to the vulva is rarely reported and usually presents as a large haematoma. The incidence of traumatic vulvar haematomas after vaginal deliveries has been reported as 1 in 310 deliveries [317]. The presence of a vulvar haematoma is closely related to an increased risk of associated vaginal, pelvic or abdominal injuries [318, 319]. Blunt injuries of the vulva and vagina are associated with pelvic trauma in 30%, after consensual intercourse in 25%, following sexual assault in 20%, and other blunt trauma in 15% [320].

*4.5.2 **Diagnostic evaluation***

4.5.2.1 Patient history and physical examination

Penile fracture is associated with a sudden cracking or popping sound, pain and immediate detumescence. Local swelling of the penile shaft develops quickly, due to enlarging haematoma [233]. Bleeding may spread along the fascial layers of the penile shaft and extend to the lower abdominal wall if Buck's fascia is also ruptured. Sometimes, the rupture of the tunica may be palpable. Less severe penile injuries can be distinguished from penile fracture, as they are not usually associated with detumescence [294].

Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting. The hemiscrotum is tender, swollen, and ecchymotic. The testis itself may be difficult to palpate. **Blunt vulvar** or perineal trauma in women may be associated with bleeding, pain and voiding problems, bladder catheterisation is usually required.

In genital trauma, a urinalysis should be performed. The presence of visible haematuria requires a retrograde urethrogram in males. In females, flexible or rigid cystoscopy is recommended to exclude urethral and bladder injury [318, 320]. In women with genital injuries and blood at the vaginal introitus, further gynaecological investigation is needed [318].

*4.5.3 **Imaging***

In cases of suspected penile fracture cavernosography, US or contrast-enhanced MRI [294, 321-323] can identify lacerations of the tunica albuginea in unclear cases [324], or provide reassurance that the tunica is intact. Magnetic resonance imaging is superior to US in diagnosing penile fracture [325]. If a concomitant urethral injury is suspected, manage as outlined in section 4.4.

Ultrasound should be performed to determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture [314, 326-334]. However, the literature is contradictory as to the usefulness of US compared to clinical examination alone. Some studies have reported convincing findings with a specificity of up to 98.6% [335]. Heterogeneous echo pattern of the testicular parenchyma with the loss of contour definition is a highly sensitive and specific radiographic finding for testicular rupture [325]. Others reported poor specificity (78%) and sensitivity (28%) for the differentiation between testicular rupture and haematocele, while accuracy is as low as 56% [327]. Colour Doppler-duplex US may provide useful information when used to evaluate testicular perfusion. If scrotal US is inconclusive, testicular CT or MRI may be helpful [336]; however, these techniques did not specifically increase the detection rates of testicular rupture.

*4.5.4 **Disease management***

4.5.4.1 Animal bites

Local wound management depends on the extent of tissue destruction. Antibiotics should be prescribed in accordance with local resistance patterns [337-339]. The possibility of rabies infection must be considered taking into account the geographical location, animal involved, specific nature of the wound and the type of attack (provoked/unprovoked). Elderly and immunosuppressed patients should be vaccinated with human rabies immunoglobulin and human diploid cell vaccine [340, 341].

4.5.4.2 Human bites

In cases of human bites, apart from wound management, infection should be considered since transmission of viral diseases may occur, Hepatitis B vaccine/immunoglobulin and/or immunodeficiency virus (HIV) post-exposure prophylaxis should be offered. For further details, see Guidelines for the Management of Human Bite Injuries [342].

4.5.4.3 Blunt penile trauma

Blunt trauma to the flaccid penis does not usually cause tearing of the tunica. Subcutaneous haematoma after sexual intercourse, without associated rupture of the cavernosal tunica albuginea, does not require surgical intervention. In these cases, non-steroidal analgesics and ice-packs are recommended [343].

4.5.4.4 Penile fracture

The thickness of the tunica albuginea in the flaccid state (approximately 2 mm) decreases in erection to 0.25-0.5 mm, and is therefore more vulnerable to traumatic injury [335, 344]. When a penile fracture is diagnosed, surgical intervention with closure of the tunica albuginea is recommended; it ensures the lowest rate of negative long-term sequelae and has no negative effect on the psychological wellbeing of the patient [345]. The approach is usually through a circumferential incision proximal to the coronal sulcus which enables complete degloving of the penis. Increasingly, local longitudinal incisions centred on the area of fracture or ventral longitudinal approaches are currently used [257]. A recent systematic review on the management of penile fractures concluded that immediate repair should be within 24 hours of presentation [346]; however, delayed presentation should not prevent exploration [297]. Further localisation may be gained with a flexible cystoscopy performed prior to incision, if urethral trauma is suspected and eventually proven [233]. Surgical closure of the tunica should be carried out using absorbable sutures.

4.5.4.5 Penetrating penile trauma

In penetrating penile trauma non-operative management is recommended for small superficial injuries with intact Buck's fascia [302]. In more significant penetrating penile injuries, surgical exploration and debridement of necrotic tissue is recommended. Even in extended injuries of the penis, primary alignment of the disrupted tissues may allow for acceptable healing because of the robust penile blood supply [306].

The principles of care are debridement of devitalised tissue, with the preservation of as much viable tissues as possible, haemostasis, diversion of urine in selected cases and the removal of foreign bodies. Tissues of questionable viability may be left for subsequent definitive surgery. If a delayed repair is needed, depending on the type of injury and the extent of tissue damage, it usually takes place four to six weeks after the trauma has occurred.

The surgical approach depends upon the site and extent of the injury, but a subcoronal incision with penile degloving usually gives good exposure. Initially, a defect in the tunica albuginea should be closed after copious irrigation. If there has been too much tissue loss, the defect can be repaired either immediately or after delay with a patch (either from an autologous saphenous vein or xenograft).

The elasticity of genital skin means it is usually possible to manage the loss of a moderate amount of penile skin; however, management is more difficult in extensive injuries with significant skin loss. The tissue chosen for reconstruction following trauma needs to provide good coverage and must be suitable for reconstruction. Split-thickness skin grafting provides good coverage and a dependable take that is reproducible and durable. However, split-thickness grafts contract more than full-thickness grafts and their

use on the penile shaft should be kept to a minimum. Skin grafts with thickness of at least 0.4 mm should be used in order to reduce the risk of contraction [306]. Full-thickness skin grafting onto the penile shaft gives less contracture, a better cosmetic appearance and more resistance to trauma during intercourse, when re-established [343]. The donor site may be taken from the abdomen, buttock, thigh or axilla and is chosen according to surgeon's preference and the pattern of injury. In cases of extensive destruction of deeper tissues, or if later prosthetic placement is being considered, skin flaps, with their secure vascular supply, can be used.

4.5.4.6 Penile avulsion injuries and amputation

Acute management involves resuscitation of the patient, and preparation for surgical re-implantation of the penis if it has been recovered and is not too badly damaged. Surgical re-implantation should be considered for all patients and should be performed within 24 hours of amputation [347].

The severed penis should be washed with sterile saline, wrapped in saline-soaked gauze, placed in a sterile bag and immersed in iced water. The penis must not come into direct contact with the ice. A pressure dressing or a tourniquet should be placed around the penile stump to prevent excessive blood loss. Re-attachment can be achieved in a non-microsurgical way, but gives higher rates of post-operative urethral stricture and more problems with loss of sensation [348]. When operating microscopically, the corpora cavernosa and urethra are firstly aligned and repaired. Subsequently, the dorsal penile arteries, the dorsal vein and the dorsal nerves are anastomosed. The cavernosal arteries are generally too small to anastomose. The fascia and skin are closed in layers and both a urethral and a suprapubic catheter are placed [349].

If the severed penis cannot be found, or is unsuitable for re-attachment, then the end should be closed as it is done in partial penectomy. Later reconstruction may be employed to lengthen the penis (e.g. suspensory ligament division and V-Y plasty, pseudo-glans formation with split-thickness skin grafting, etc.). A delayed major reconstructive procedure, i.e. phalloplasty (either radial artery or pubic), is sometimes required for injuries which leave a very small or non-functioning penile stump [347].

4.5.4.7 Testicular dislocation

It can be either a subcutaneous dislocation with epifascial displacement of the testis or an internal dislocation. In the latter, the testis is positioned in the superficial external inguinal ring, inguinal canal or abdominal cavity. Traumatic dislocation of the testis is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated.

4.5.4.8 Haematocoele

Conservative management is recommended in haematoceles smaller than three times the size of the contralateral testis [350]. In large haematoceles, non-operative management can fail, and delayed surgery (more than three days) is often required. Patients with large haematoceles have a higher rate of orchiectomy than patients who undergo early surgery, even in non-ruptured testes [285, 306, 313, 351, 352]. Early surgical intervention results in preservation of the testis in more than 90% of cases compared to delayed surgeries which result in orchiectomy in 45-55% of patients [313]. In addition, non-operative management is also associated with prolonged hospital stays. Therefore, large haematoceles should be treated surgically, irrespective of the presence of testicular contusion or rupture. At the very least, the blood clot should be evacuated from the tunica vaginalis sac to relieve disability and hasten recovery.

4.5.4.9 Testicular rupture

It is essential to surgically explore equivocal patients whenever imaging studies cannot definitively exclude testicular rupture. This involves exploration with evacuation of blood clots and haematoma, excision of any necrotic testicular tubules and closure of the tunica albuginea, usually with running 3.0-absorbable sutures.

4.5.4.10 Penetrating scrotal trauma

Penetrating injuries to the scrotum require surgical exploration with debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of the testis and scrotum can usually be performed. In complete disruption of the spermatic cord, re-alignment without vaso-vasostomy may be considered if surgically feasible [353]. Staged secondary microsurgical vaso-vasostomy can be performed after rehabilitation, although only a few cases have been reported [353]. If there is extensive destruction of the tunica albuginea, mobilisation of a free tunica vaginalis flap can be performed for testicular closure. If the patient is unstable or reconstruction cannot be achieved, orchiectomy is then indicated. Prophylactic antibiotics are recommended after scrotal penetrating trauma, although data to support this approach are lacking.

Extended laceration of scrotal skin requires surgical intervention for skin closure. Due to the elasticity of the scrotum, most defects can be primarily closed, even if the lacerated skin is only minimally attached to the scrotum [306]. Local wound management with extensive initial wound debridement and washout is important for scrotal convalescence. In the case of extensive loss of genital tissue, e.g. improvised explosive device blast injury, complex and staged reconstructive surgical procedures are often required [304].

Table 4.5.1: Summary of key points for penile fracture and testicular trauma

Summary of key points:
Penile fracture
The most common causes of penile fracture are sexual intercourse, forced flexion, masturbation and rolling over.
Penile fracture is associated with a sudden cracking or popping sound, pain, immediate detumescence and local swelling.
Magnetic resonance imaging is superior to all other imaging techniques in diagnosing penile fracture.
Management of penile fracture is surgical intervention with closure of the tunica albuginea.
Testicular Trauma
Blunt testicular injury may occur under intense compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea.
Testicular rupture is associated with immediate pain, nausea, vomiting, and sometimes fainting.
Scrotal ultrasound is the preferred imaging modality for the diagnosis of testicular trauma.
Surgical exploration in patients with testicular trauma ensures preservation of viable tissue when possible.

*4.5.5 **Complications***

The possibility of complications from genital trauma, including psychological effects, erectile dysfunction, urethral stricture, and infertility, is high. In patients with a history of penile fracture post-operative complications were reported in up to 20% of cases, development of plaques or nodules following surgery, post-operative curvature formation and erectile dysfunction occur in 13.9%, 2.8% and 1.9% of patients, respectively [294]. Post-surgical erectile dysfunction is more common in patients > 50 years and those with bilateral corporal involvement [354]. Skin necrosis is rare [297]. Conservative management of penile fracture increases complications, such as penile abscess, missed urethral disruption, penile curvature, and persistent haematoma requiring delayed surgical intervention [355]. Late complications after conservative management were fibrosis and angulations in 35% and impotence in up to 62% [296, 356].

Post-operative complications were reported in 8% of patients who underwent testicular repair after penetrating trauma [302]. Despite good management and regular follow-up of external genital gunshot wounds, such wounds are fraught with the possibility of complications such as erectile dysfunction, urethral stricture, and infertility. Delayed complications include chronic pain and testicular atrophy. Haematoceles initially treated non-operatively may eventually need delayed surgery if they develop infection or undue pain. Genital injuries are rarely life threatening, but fertility and testosterone production often become the male trauma patient's chief concern once acute issues are resolved [357].

*4.5.6 **Follow-up***

In patients with genital trauma follow-up should focus on diagnosis of and therapy for late complications. Erectile dysfunction, urethral stricture and assessment of fertility are the main concerns [300, 358].

*4.5.7 **Summary of evidence and recommendations for evaluation and management of genital trauma.***

Summary of evidence	LE
A concomitant urethral injury complicates penile fractures and requires specialised management.	3
Ultrasound can determine intra- and/or extra-testicular haematoma, testicular contusion, or rupture with heterogeneous echo pattern parenchyma and loss of contour definition a highly sensitive and specific finding.	3
Surgical treatment of penile fracture ensures the lowest rate of negative long-term sequelae on functional and psychological wellbeing of the patient.	3
In patients with testicular rupture or equivocal imaging, surgical exploration can secure preservation of viable tissue.	3

Recommendations	Strength rating
Exclude urethral injury in the case of penile fracture.	Strong
Perform ultrasound (US) for the diagnosis of testis trauma.	Strong
Treat penile fractures surgically, with closure of tunica albuginea.	Strong
Explore the injured testis in all cases of testicular rupture and in those with inconclusive US findings.	Strong

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6. CONFLICT OF INTEREST

All members of the Urological Trauma Guidelines working group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

7. CITATION INFORMATION

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